THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON CAPNELLANE

by

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A THESIS

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TO KOU-JONG AND MY PARENTS

ABSTRACT

Recently, a number of sesquiterpenoids possessing the novel carbon skeleton of Capnellane (1) have been isolated from a marine source. This thesis describes a highly stereoselective synthesis of aldehyde 62, a potential synthetic precursor of 1.

Photocycloaddition of 4-acetoxy-2-cyclopenten-1-one to vinyl acetate followed by treatment of the adduct with p-toluenesulfonic acid gave rise to an epimeric mixture of enones 14. 1,4-Addition of a methyl group to 14 was accomplished using either lithium dimethylcuprate or a methyl magnesium bromide-cuprous iodide complex. The epimeric mixture of keto acetates 15 thus obtained was hydrolyzed with aqueous sodium carbonate and the resulting alcohols treated with 1,2-ethanedithiol and boron trifluoride to give two epimeric thioketals 23 and 23a. Oxidation of these two epimers with acetic anhydride and dimethyl sulfoxide gave the same cyclobutanone 24. Boron trifluoride catalyzed ring expansion of 24 with ethyl diazoacetate gave keto ester 25 contaminated by a small amount of its positional isomer 26. Subsequent alkylation of this mixture with 1-bromo-3-methyl-2-butene afforded two separatable olefins 52 and 53 with the former isomer predominating. Lithium aluminum hydride reduction of 52 followed by Moffatt oxidation of the resulting diol 54 yielded keto aldehyde 55 whose selective thioketal formation gave rise to ketone 56. Raney nickel treatment of 56 effected simultaneous removal of its thioketal groups. This enone was subsequently reduced to alcohol 59 and the latter

compound acetylated to give acetate 61. Selenium dioxide oxidation of 61 resulted in the formation of aldehyde 62.

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INTRODUCTION

As a consequence of the rapid development of marine chemistry in recent years, a vast number of novel natural products have been isolated from marine sources[1] and many of these compounds shown to possess structural types differing from those available from non-marine origins. Two years ago, Djerassi and Tursh and their co-workers[2] reported the isolation from Capnella imbricata, a soft coral indigenous to Indonesia area, of several sesquiterpenoids derived from the new skeleton of Capnellane (1). The structure and absolute configuration of one of them, $\Delta^{9(12)}$capnellene-$3\beta,8\beta,10\alpha$-triol (2) have been fully established by chemical and spectral studies and by a single crystal X-ray crystallographic analysis. In addition to its novel carbon framework, the naturally occurring triol 2 possesses the unusual enediol system in its C-ring. These two intriguing structural features also represent, from a synthetic point of view, challenging problems. As the first-stage studies toward the total synthesis of 2, we have focused our attention to the construction of its parent hydrocarbon capnellane (1).

The occurrence of tricyclo[$6.3.0.0^{2,6}$]undecane ring system in nature is rare. Prior to the isolation of 2 and its related compounds*, only few fungal metabolites of the hirsutic acid (3)[3] family were known to display such a system. Existing methods for its synthesis are also limited. Hirsutic acid (3) and its unnatural isomer isohirsutic acid

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* Details of their structures are yet to be reported.

(4) have been synthesized by Matsumoto et al.[4], and by Lansbury et al.[5,6], respectively. The methods demonstrated in those syntheses are however inadequate for the present purpose by virtue of the fact that the capnellane skeleton differs greatly from the hirsutic acid skeleton in substitution patterns.

Prior to the present studies, a general approach to the synthesis of hydrindanonecarboxylates[7] has been developed in this laboratory. As illustrated in Scheme I with isophorone (5), the synthesis involves an enone photoannelation as a general entry for the construction of a suitably substituted bicyclo[4.2.0]octan-7-one system (5→6) and the boron trifluoride catalyzed ring expansion of its cyclobutane ring with ethyl diazoacetate* as a key step (6→7). During the course of those and the related studies[15], it was also found that, in cases of unsymmetrically substituted cycloalkanones, such as 6, the ring expansion reaction proceeded with a high degree of regioselectivity[7,15]. Without any exception the migratory apptitude was shown to be such that, in contrast to the known rearrangement reactions[16], the less substituted α-carbon migrates predominantly or exclusively.

In principle, the above synthetic approach to hydrindanonecarboxylates could be extended to the preparation of bicyclo[3.3.0]octane derivatives using 2-cyclopenten-1-ones in place of 2-cyclohexen-1-ones

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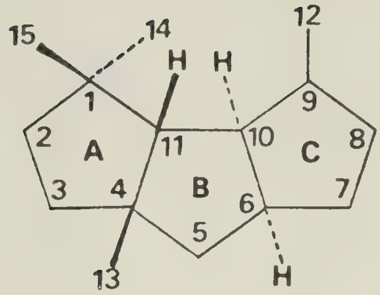
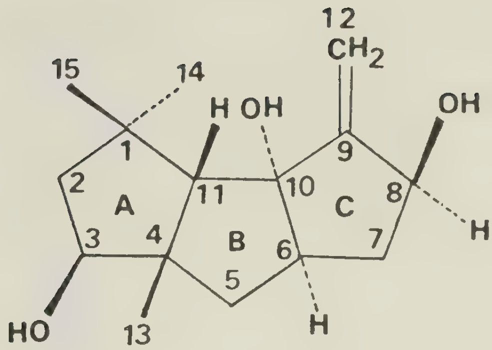
*For other examples of Lewis acid catalyzed ring expansion of cycloalkanones with diazoacetate see references 9-15.



1



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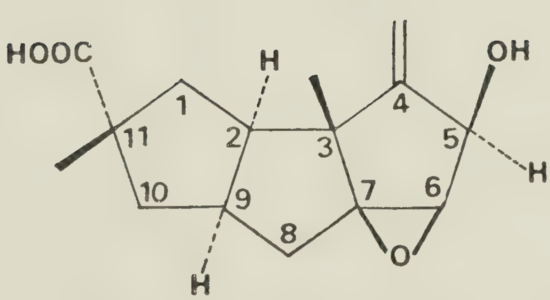

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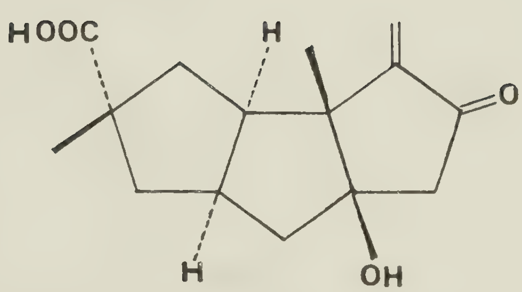

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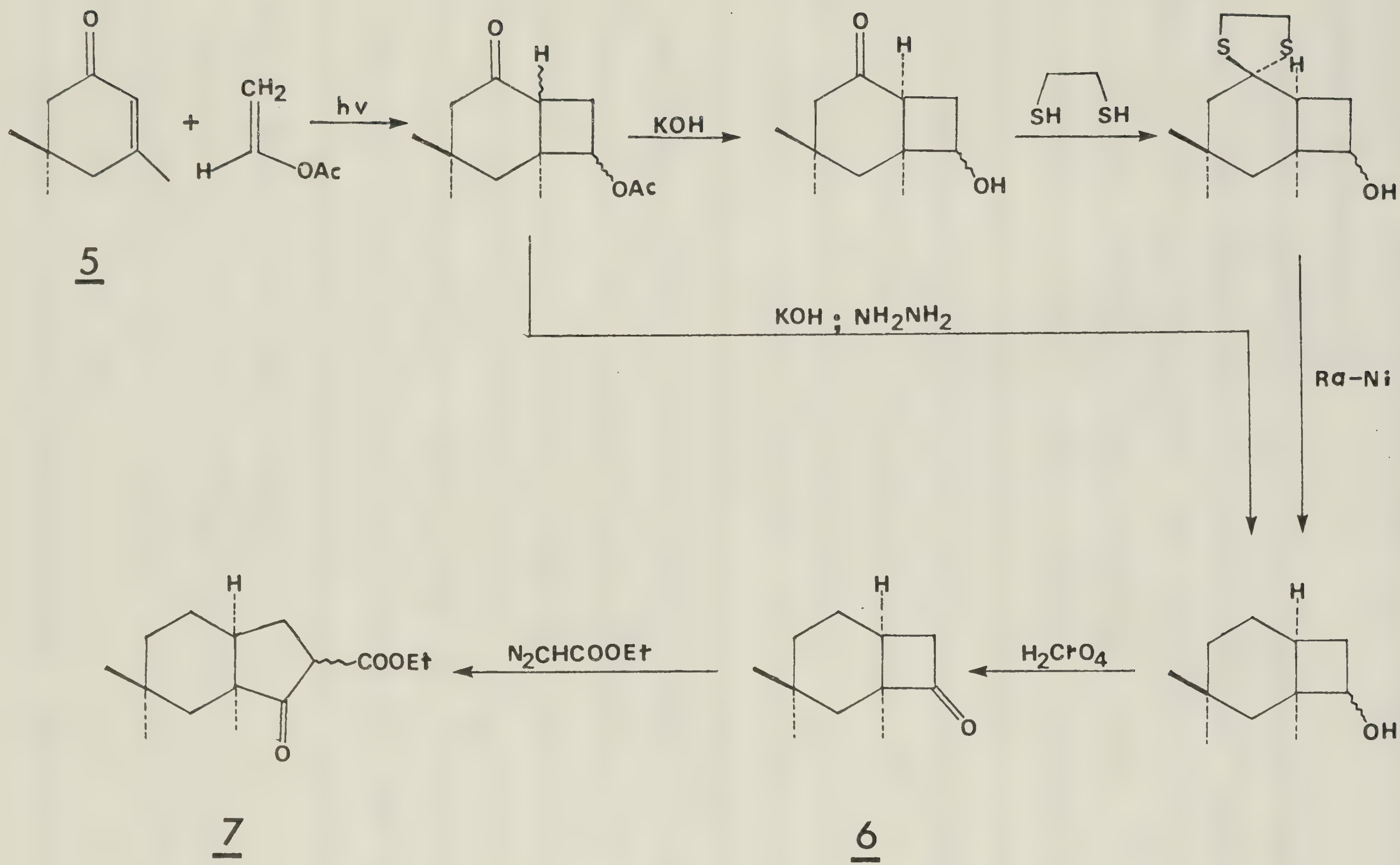

CH2
OAc
hv
H
O
OAc
KOH
OH
SH SH
S S
KOH ; NH2NH2
Ra-Ni
H2CrO4
N2CHCOOEt
COOEt
5
6
7

SCHEME I

as starting materials. Such an extension should prove highly applicable in the synthesis of capnellane (1).

The photocycloaddition of 2-cyclopenten-1-one to vinyl acetate for instance, is expected to proceed in a head-to-tail manner[8] to give photo-adduct 8 with a cis ring juncture*. The conversion of 8 to type 9 could be conceivably achieved by simple modifications of its functionalities similar to those described in Scheme I. Subsequent ring expansion of 9 with ethyl diazoacetate and boron trifluoride is expected to give 10 as the predominant (possibly to an exclusive extent) product. The similarity of 10 and the B,C ring system of capnellane (1) is apparent; other than lacking a methyl group, 10 contains all the required features of the B and C rings of 1. Furthermore, the β-keto ester group of 10 is highly suitable for further construction of the remaining A ring.

Ring A could be formed involving an overall process of incorporating an "isopentenyl unit" to C_2 and C_3 of 10 using the existing functionalities in a manner as indicated in formula 11. Alternatively, it could be annelated by adding the required unit to C_3 and C_4 of 10 as indicated in 12 by further activating the C_4 center such as by introducing a C_3-C_4 double bond. Pending on the mode of A ring formation, the ring C methyl of the target molecule 1 is required to be placed, in the former case, at C_8 of 10 and, in the later, at its C_6.

In view of that the approach indicated in 11 needs less disturbance of the existing functional groups, it was chosen at the outset as the means

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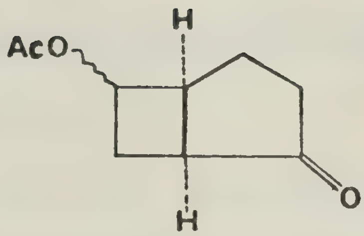
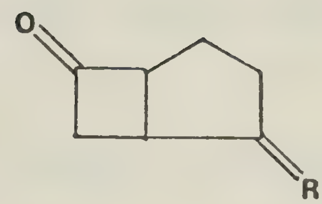
*A trans arrangement in bicyclo[3.2.0]heptane system is sterically forbidden.



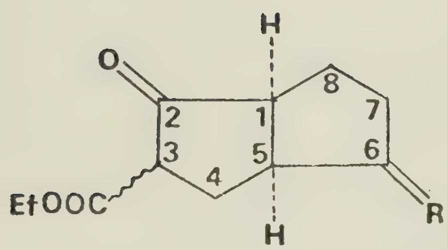
AcO
H
H
O

8



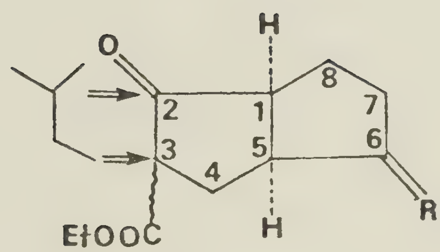
O
R

9



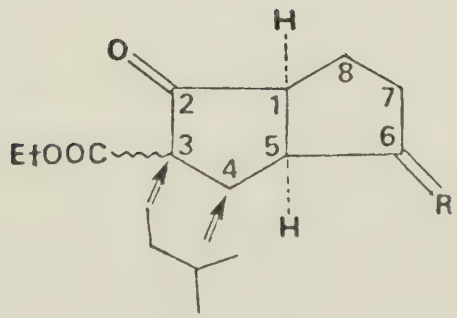
H
O
2
1
8
7
3
5
6
4
EtOOC
H
R

10



H
O
2
1
8
7
3
5
6
4
EtOOC
H
R

11



H
O
2
1
8
7
EtOOC
3
5
6
4
H
R

12

for the formation of ring A. Consequently, it required a device to facilitate the incorporation of a methyl substituent to C_8 of 10. This task could be conceivably achieved without difficulties by a suitable choice of the starting enone.

The above considerations constitute the framework of the synthetic studies on capnellane (1) described in this thesis.

RESULTS AND DISCUSSION

In order to facilitate the incorporation of the ring C methyl substituent of capnellane (1), 4-acetoxy-2-cyclopenten-1-one[17-19] was chosen as the starting material. Its photocycloaddition to vinyl acetate in benzene proceeded in a highly regioselective manner to give photo-adduct 13 as a mixture of diastereomers. Due to its instability*, 13 could not be obtained in pure state. Its structural assignment follows unambiguously from the subsequent transformations. Treatment of 13 with a catalytic amount of p-toluenesulfonic acid in benzene afforded enone 14 in 74% yield from the starting enone. Although 14 was found to be homogeneous on thin-layer chromatography, the presence of both the endo (14a) and the exo (14b) epimers was evident from the nuclear magnetic resonance (nmr) spectrum which displayed two sets of signals** in accord with the structures of 14a and 14b in a ratio of ca. 10 : 7. Furthermore, an examination of Dreiding models revealed that in the case of the exo epimer 14b, the methine proton adjacent to the acetoxy group lies within the shielding zone of the double bond and its appearance in a higher field in the nmr spectrum was expected. The fact that this hydrogen atom resonated as a multiplet at an abnormally high field of τ 5.50 as a part

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*An attempted purification of 13 by column chromatography on silica gel resulted in its partial decomposition to give 14. A similar result was obtained when its purification was attempted by distillation.

**See experimental section for details.

of the minor nmr signals strongly suggested that 14b was the minor component. Since the chiral carbon bearing the acetoxy group would be destroyed in a later stage, no attempt was made to separate these two epimers.

The required ring C methyl group of 1 was subsequently incorporated by a 1,4-addition process. Initially the reaction was carried out using lithium dimethylcuprate as a reagent. Under standard reaction conditions[20], treatment of the epimeric mixture of 14 with lithium dimethylcuprate gave, in addition to the desirable acetate 15 in 50% yield, a substantial quantity (21%) of β-diketone 16. The infrared (ir) spectrum of 15 showed the absence of the conjugated enone absorptions and a broad band at 1735 cm^{-1} diagnostic for both the ester and the cyclopentanone groups. In the mass spectrum, a molecular ion peak at 182.0945 was in agreement with the molecular formula of $C_{10}H_{14}O_3$. The stereochemistry of 15 was assigned as follows. The nmr spectrum of 15 displayed, in addition to a singlet at τ 8.0 for the acetyl group, two methyl doublets at τ 8.98 and 9.02 for a total of three protons suggesting the presence of at least two stereoisomers. The stereochemical heterogenity of 15 could be logically attributed, in part at least, to the inheritance of that of the starting material since epimers of 14 were used. Furthermore, the 1,4-addition reaction was expected on the basis of a large number of precedants[20-24] to proceed favorably from the sterically less hindered convex side of the molecule resulting in the depicted stereochemistry for the newly formed chiral center. Although the magnitude of selectivity could not be ascertained at this stage, the subsequent transformations of 15 showed that, when the pre-existing chiral center C_6 was destroyed, a single compound was obtained (vide infra). These later findings clearly indicated that 15 contained only a pair of C_6 epimers and that the 1,4-addition

reaction proceeded stereoselectively to an exclusive extent*. The structure of the minor product 16 (existing partially in its enol form(s)) could be readily deduced on the basis of its spectral data. The ir spectrum showed absorption bands at 3450, 1725 and 1640 cm^{-1} for the hydroxyl group, the ketone carbonyls and the chelated β-hydroxy α,β-unsaturated ketone moiety[25] respectively. In the nmr spectrum, a methyl doublet and an acetyl singlet appeared respectively at τ 8.95 and 7.98. The structural assignment was further confirmed by acetylation. The product 18 thus obtained showed in the ir spectrum, in addition to the characteristic chelated β-hydroxy α,β-unsaturated ketone bands at 3460, 1655 and 1620 cm^{-1}, an intense ester carbonyl absorption at 1738 cm^{-1}. The formation of 16 could be attributed to an intramolecular transformation of an acyl group involving the intermediacy of the enolate ion 19** resulting from the initial 1,4-addition. This transformation was anticipated to proceed with ease due to the close proximity of the endo acetoxy group and the carbanion. In agreement with the involvement of an intramolecular process was the fact that no dectectable amount of acetate 18 and/or its C_6 epimer was obtained

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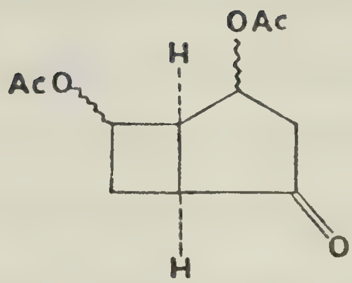
*At present, the stereochemistry of capnellane (1) at C_9 is not of crucial importance since triol 2, the only member of the capnellane family whose structure has been concluded, possesses a double bond at this site. For practical purpose however, it is highly desirable to secure its homogenity.

**The transformation of an exo acetyl group is sterically forbidden.

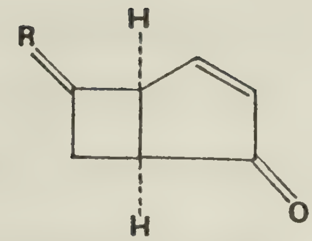
from the reaction mixture; should an intermolecular process be involved, the formation of such compounds would be highly probable. On the basis of these assumptions, the stereochemistry of 16 could be tentatively assigned as shown.

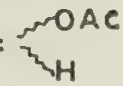
In an effort to avoid the formation of 16, the 1,4-addition reaction was subsequently carried out using the complex generated from methylmagnesium bromide and cuprous iodide in place of lithium dimethylcuprate. Although this method did not suppress the production of 16 nor improved the yield of the desirable acetate 15 greatly, it was shown to be superior than the previous one in that the results were reproducible irrespective of the preparative scale.

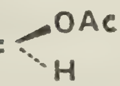
Subsequent hydrolysis of 15 using aqueous sodium carbonate in methanol resulted in the formation of the epimeric keto alcohols 20 in 64% yield. The ir spectrum of 20 showed the characteristic hydroxy and cyclopentanone carbonyl absorption bands at 3430 and 1730 cm^{-1}, respectively. In the nmr spectrum, the methyl groups of the two epimers appeared as a single doublet at τ 9.02 and the methine protons adjacent to the hydroxyl groups were found as a multiplet centered at τ 5.89. A molecular ion at 140.0814 in the mass spectrum was in further support of the structural assignment. It was noted that in principle diketone 16 could also be converted into the desirable 20 (with α-OH) by removing its acetyl group under reaction conditions similar to those used for the hydrolysis of 15. Experimentally, this was found to be not the case. When a mixture of 15 and 16 directly obtained from the 1,4-addition reaction was treated with aqueous sodium carbonate in methanol, 16 was

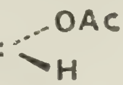


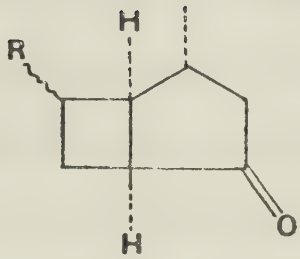
13



14 R = 

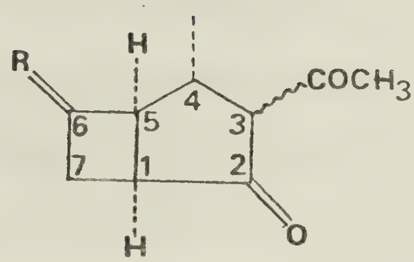
14a R = 

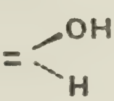
14b R = 

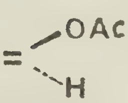


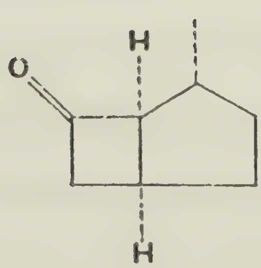
15 R = OAc

20 R = OH

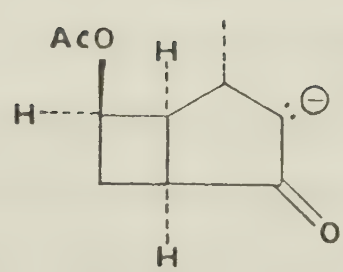


16 R = 

18 R = 



17



19

converted largely to 21 as a result of the selective cleavage of its cyclopentanone ring by methoxy ion. Although rather unusual, such a selectivity could be attributed to the ring strain of the system.

Since the modification of the cyclobutane ring of 20 to the required five-membered B ring of capnellane (1) would proceed by ring expansion of a cyclobutanone intermediate, it was desirable to either remove or protect the existing carbonyl in advance in order to prevent any complication due to the presence of two ketones. The direct removal of the ketone carbonyl of 20 could be achieved by Wolff-Kishner reduction[26] using Huang-Minlon's modification[27]. The yield of alcohol 22 (probably a mixture of two epimers) thus obtained was however low. In spite of several attempts made to improve the yield, the best obtained was 32%. Subsequent treatment of 22 with Jones reagent affected its oxidation to give ketone 17. This ketone was found to be extremely volatile and its attempted purification by column chromatography resulted in substantial loss of the material. A 61% yield of 17 of satisfactory purity could however be obtained by distillation using a Kugelrohr apparatus.

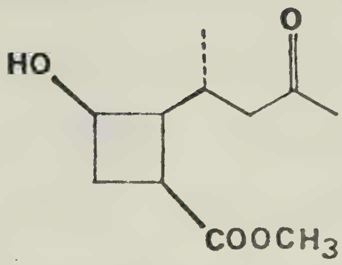
By virtue of the facts that the yield of 22 was unsatisfactory and that 17 was difficult to handle, our attention was drawn to the protection of the carbonyl group of ketol 20. As the total synthesis of 1 requires ultimately its removal, thioketal was chosen as the blocking group. Treatment of 20 with 1,2-ethanedithiol in the presence of boron trifluoride etherate resulted in the formation of two alcohols 23 and 23a in ca. 1 : 2 ratio and in a total yield of 94%. These two alcohols

were readily separatable by column chromatography on silica gel. The ir spectrum of the minor and faster-moving isomer 23 showed a hydroxy absorption band at 3345 cm^{-1}. Its nmr spectrum displayed a doublet at τ 8.87 and a multiplet at τ6.82 for the methyl substituent and the thioketal group respectively. The same chemical shifts and the same splitting patterns were observed for the corresponding groups of the major isomer 23a in its nmr spectrum. In the ir spectrum, 23a showed an absorption band for its hydroxyl group at 3320 cm^{-1}. The structural assignments as well as the isomeric relationship of these two alcohols were further verified by their mass spectra displaying in each case a molecular ion peak at 216.0651. Although not of crucial importance, their stereochemistry could be tentatively assigned on the basis of their differences in affinity for silica gel.

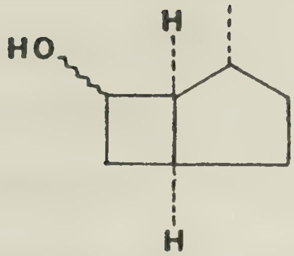
When 23a was subsequently subjected to the treatment of dimethyl sulfoxide and acetic anhydride[28,29] at ≈3°C for six days, the oxidation occurred smoothly to give a 79% yield of cyclobutanone 24 whose structure was evident from its ir spectrum showing the diagnostic four-membered ketone absorption at 1777 cm^{-1}. In the nmr spectrum, a methyl doublet appeared at τ 8.81 and a four-proton multiplet centered at τ 6.73 was observed for the thioketal methylenes. A molecular ion peak at 214.0485 in the mass spectrum was in agreement with the required molecular formula $C_{10}H_{14}OS_2$. Under the same conditions used for the oxidation of pure 23a, the mixture of 23 and 23a reacted with dimethyl sulfoxide and acetic anhydride to give an 85% yield of 24 and no detectable amount of its C_4 epimer. The formation of 24 as the only diastereomer provided conclusive evidence that 23 and 23a must be epimeric at the chiral

center bearing the hydroxyl group. Extention of this conclusion further required precursors 15 and 20, in each case, a pair of C_6 epimers with complete stereochemical integrity at C_4. Consequently, the 1,4-addition reaction of 14 must have proceeded in a completely stereoselective fashion.

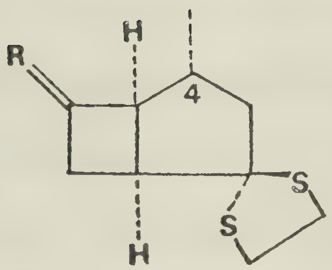
Homologation of the cyclobutanone ring of 24 to provide ring B of the target molecule 1 was achieved using the method developed in this laboratory[7]. Treatment of 24 with ethyl diazoacetate and boron trifluoride in ether at -35°C for twenty minutes, the reaction proceeded smoothly to give an 85% yield of the ring expansion product which was shown to be homogeneous by both gas chromatography and thin-layer chromatography. The gross structure (i.e. 25 and/or 26) of the product was readily deduced on the basis of the following spectroscopic analyses. The ir spectrum showed absorption bands at 3400, 1745, 1718, 1650 and 1610 cm^{-1} diagnostic for the cyclopentanone carboxylate system existing partially in the enol form. A molecular ion peak at 300.08541 in the mass spectrum was in full agreement with the required molecular formula of $C_{14}H_{20}O_3S_2$. Although in agreement with the gross structural assignment, the nmr spectrum was rather complex. It displayed a methyl doublet at τ 8.81, two triplets at τ 8.72 and 8.74 and two quartets at τ 5.81 and 5.87 for the carbethoxy group, and two singlets at τ 6.74 and 6.81 for the thioketal group. The complexity of the nmr spectrum could be either due to the co-existence of 25 and its enol form 25a or that of



<u>21</u>



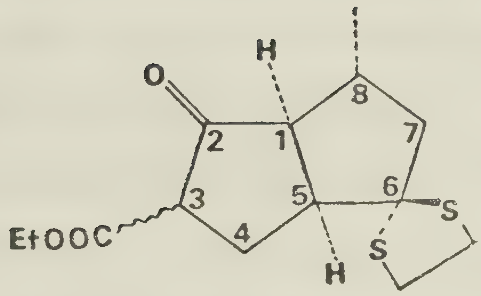
<u>22</u>



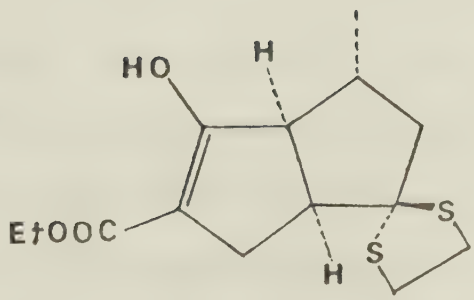
<u>23</u> R = OH, H

<u>23a</u> R = H, OH

<u>24</u> R = O



<u>25</u>



<u>25a</u>

a pair of 26 and 26a* or due to the presence of both 25 and 26 and their corresponding enols. As the detailed structure(s) of the ring expansion product(s) could not be unambiguously determined by spectroscopic methods, attention was drawn to alternative means to solve the problem. The following chemical transformations were carried out and on the basis of these results, it was concluded that the ring expansion product, although homogeneous by thin-layer and gas chromatographic analyses, was in fact a mixture of the desirable keto ester 25 and its positional isomer 26 in a ratio of ca. 4 : 1 with the former predominating.

Sodium borohydride reduction of the ring expansion product gave, in a 4 : 1 ratio, two separatable alcohols which were independently acetylated with acetic anhydride in pyridine to give two isomeric acetates. The structure of the acetate obtained from the minor alcohol could be readily assigned as 30 and thus that of its immediate precursor 28 on the basis of its nmr spectrum which showed a triplet of a doublets at τ 5.72 for the methine proton adjacent to the acetoxy group. On the other hand, The nmr spectrum of the other acetate showed a doublet of doublets at τ 4.71 for the corresponding hydrogen atom. This coupling pattern could be better explained by the structure of 29

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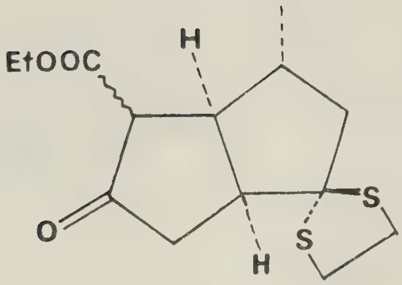
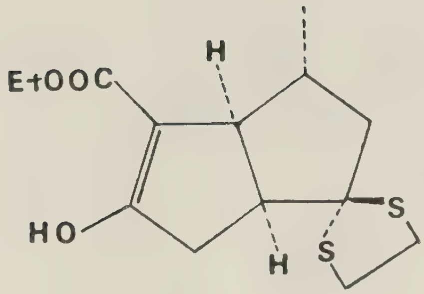
*Although the presence of this pair along was highly unlikely since the migratory apptitude of the boron trifluoride catalyzed ring expansion of unsymmetrically substituted cycloalkanones with ethyl diazoacetate was shown to involve mainly the less substituted α-carbon[7,15], it was nevertheless a possibility.

but by no means conclusive since it could also arise from a stereoisomer of 30 with a zero coupling between the proton in question and one of the three adjacent hydrogen atoms. The latter possibility was ruled out as follows. Treatment of 30 with sodium hydride and a small amount of t-amyl alcohol in 1,2-dimethoxyethane resulted in the formation of the α,β-unsaturated ester 32. Under the same conditions, the major acetate also underwent elimination to give an α,β-unsaturated ester which was found to be isomeric with but different from 32 and to which structure of 31 could be readily assigned. Accordingly, its two precursors, acetate and alcohol, must possess structures 29 and 27 respectively. It was clear, on the basis of these results, that the ring expansion product must be a mixture consisting of 25 as the chief component and 26 in minor quantity. Since 25 was inseparatable from 26, for the subsequent transformation, the mixture was used and it was hoped that the products could be resolved at an appropriate stage.

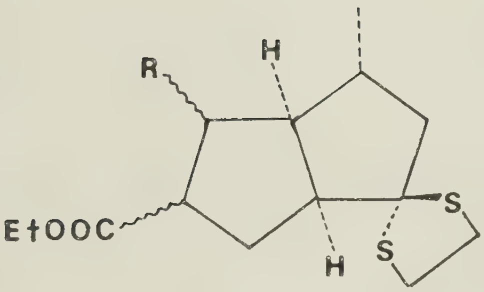
Although not in a pure state, the formation of 25 having all the required features of the B,C ring system of 1 and proper functionalities for annelating the remaining A ring completed our first stage synthetic goal. One of the simple approaches to ring A formation could be envisaged as outlined in Scheme II. In principle, alkylation of 25 with 1-bromo-2-butanone followed by Aldol condensation of the resulting dione 33 could give rise to enone 34 of which metal reduction followed by trapping the enolate ion thus formed with methyl halide (34 → 35) could result in the completion of the framework of the target molecule 1. Since 1-bromo-2-butanone was less accesible, bromoacetone[30] was first used as a model to test the feasibility of such a scheme. Treat-



26

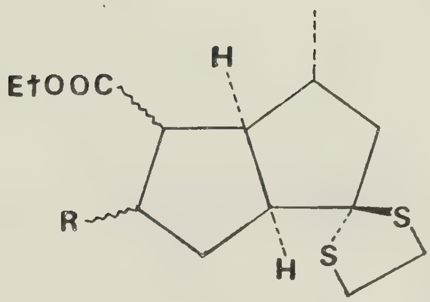


26a



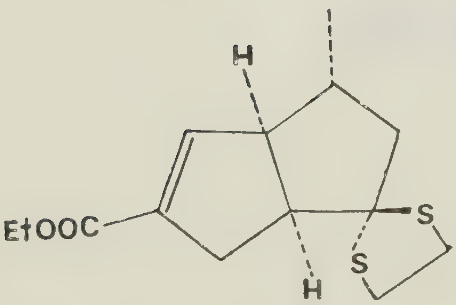
27 R = OH

29 R = OAc



28 R = OH

30 R = OAc



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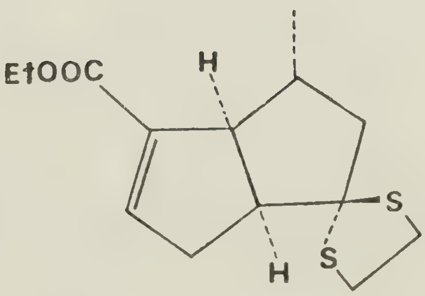

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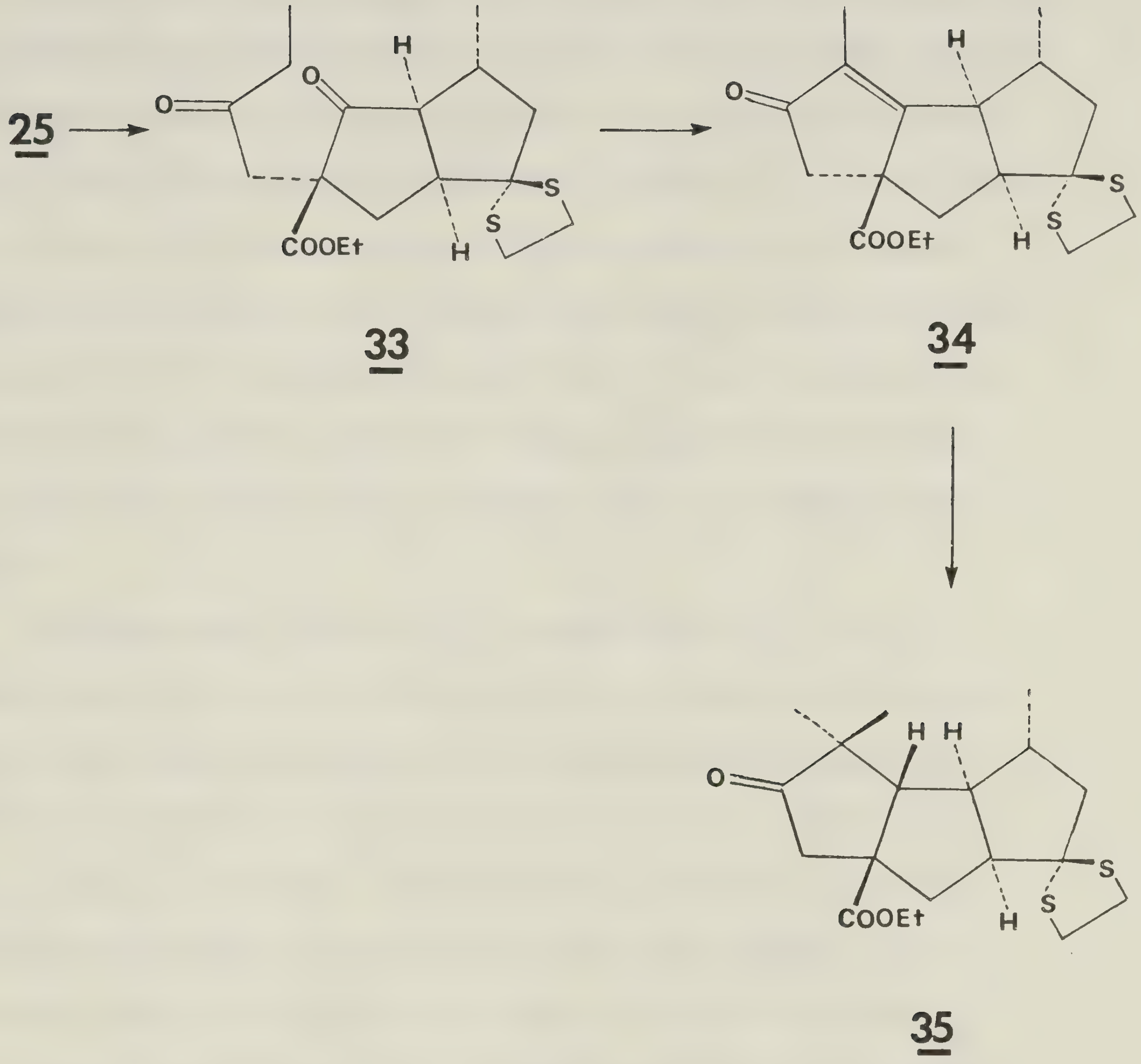


SCHEME II

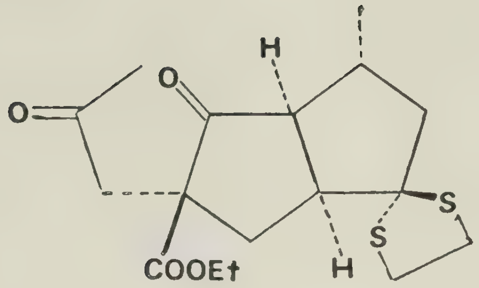
ment of the mixture of 25 and 26 with sodium hydride followed by addition of bromoacetone gave a 79% yield of a mixture of two alkylation products as indicated by the nmr spectrum displaying two methyl ketone singlets at τ 7.92 and 8.0, as well as two thioketal singlets at τ 6.75 and 6.79. Since a mixture of 25 (predominant) and 26 was used as the reactant and since the alkylation of each molecule was highly likely to proceed from the sterically less hindered vertex face, it could be tentatively concluded that the mixture consisted of 36 and 37 with the former as a major component. Efforts made to separate these two compounds were fruitless.

Attempted cyclization of 36 (contaminated by 37) using p-toluenesulfonic acid resulted in the complete recovery of the starting mixture. On the other hand, under basic conditions (sodium hydride—t-amyl alcohol), the mixture reacted but no detectable amount of the desired product was formed. The major product obtained showed the absence of ethoxy signals in the nmr spectrum. Its formation thus required the ejection of such a group likely via a Claisen condensation reaction. Accordingly, its structure was tentatively assigned as 38 or 39 or a mixture of both. One of the possibilities to circumvent the complications caused by the ester group was to convert it to the angular methyl substituent of 1 prior to the ring closure. Towards this end, ketalization of the two ketone carbonyls of 36 was attempted. Under a variety of reaction conditions, however, only its side chain ketone carbonyl was affected. For instance, heating a mixture of 36 and 37 at reflux with ethylene glycol and p-toluene-

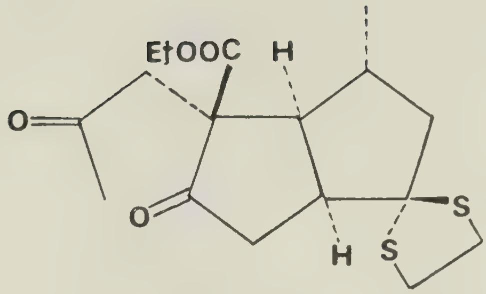
sulfonic acid in benzene gave quantitatively and exclusively monoketals 40 and 41 as an inseparatable mixture. Because of the unfavorable results of these experiments, the route outline in Scheme II was abandoned and an alternative approach was sought.

The above findings indicated that the direct formation of a five-membered ring was difficult to achieve by an Aldol condensation. Other than the observed complications caused by the ester group, the reluctance of 25 to undergo the desirable cyclization might have been due to additional angular strain induced by ring closure. The formation of a six-membered ring, which should not cause any major disturbance to the system in that respect, might take a different course. Under these consideration, it was thought to proceed the synthesis by first constructing a homo-system 42 using a Robinson annelation reaction with ethyl vinyl ketone as indicated in Scheme III. Metal reduction of the enone moiety followed by trapping the enolate ion so generated with a methyl halide would allow the incorporation of an additional methyl group specifically to the desirable site (42 → 43). Subsequent ring contraction (43 → 44) would then provide the parent skeleton of 1.

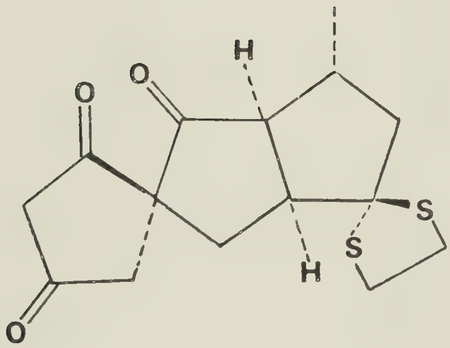
Treatment of 25 with ethyl vinyl ketone and sodium hydride gave, in addition to 23% of the recovered starting material, a 42% yield (on the basis of the consumed material) of a mixture of 45 and 46 inseparatable by column chromatography. The structures of alkylated products 45 and 46 were evident from the spectral data. The ir spectrum showed absorption bands at 1710 cm^{-1} for the side chain



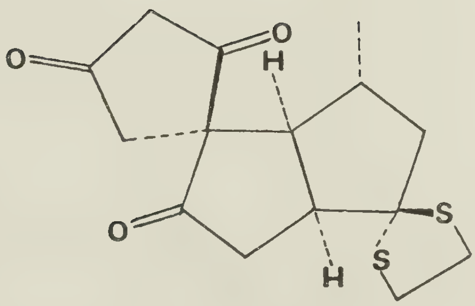
36



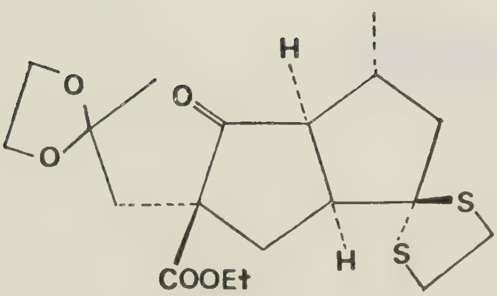
37



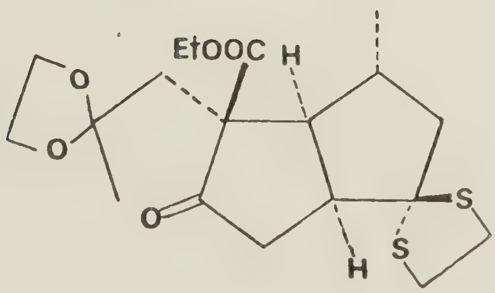
38



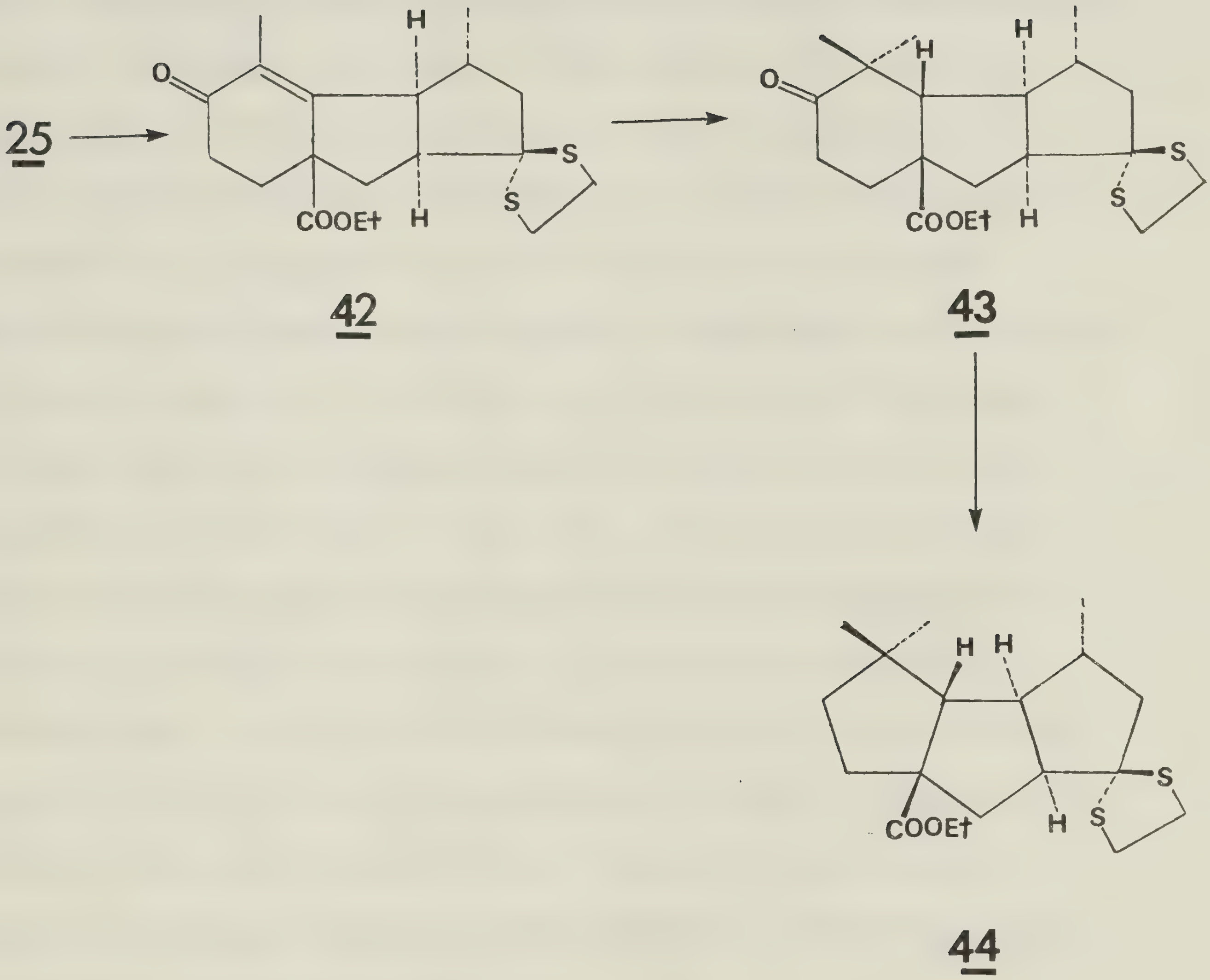
39



40



41



SCHEME III

ketone and 1742 cm^{-1} for the cyclopentenone and the ester carbonyls. The nmr spectrum displayed two methyl doublets at τ 9.00 and 9.04 strongly suggested a mixture of two isomers*. The mass spectrum displayed a molecular ion peak at 384.1433 in agreement with the structural assignments. Attempted cyclization of this material was however uneffected under a variety of conditions. In order to remove any unfavorable effects which might have been caused by the thioketal group, the mixture of 45 and 46 was subjected to Raney nickel treatment. The desulfurization reaction also resulted in the reduction of the side chain ketone carbonyl as indicated by the ir spectrum of the product which showed hydroxyl absorption and the disappearance of the band corresponding to that ketone. Consequently, the product without purification was oxidized with Jones reagent. The material (probably a mixture of 47 and 48) thus obtained was subsequently treated with p-toluenesulfonic acid in refluxing benzene to effect its cyclization. A yield of 43% of 49 and/or 50 was obtained. The gross structure of the product was established as follows. The methyl group attached to the double bond appeared in the nmr spectrum at τ 8.18 as a singlet.

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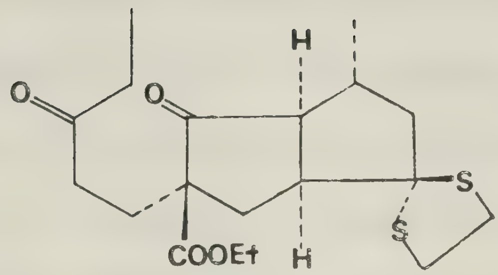
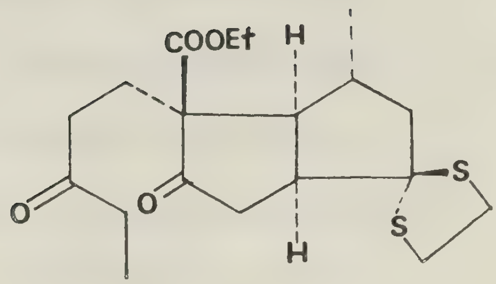
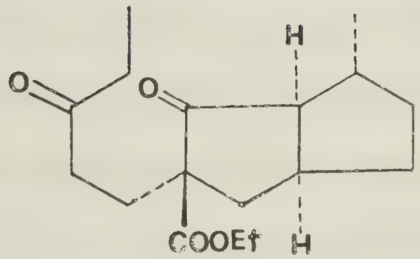
*The possibility of that the two compounds were stereoisomers of either 45 or 46 could not be excluded. The positional isomers were tentatively assigned on the grounds that both 25 and 26 were present in the starting material and that the Michael addition was expected to occur in both cases from the less hindered *exo* side.



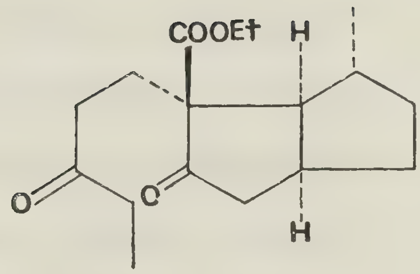
45



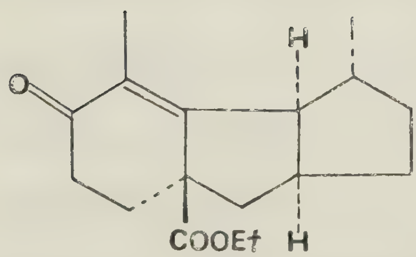
46



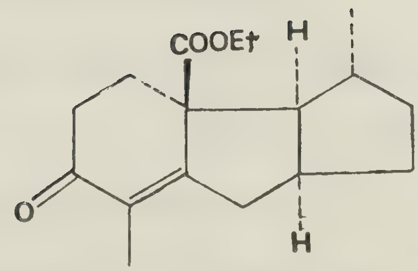
47



48



49



50

The ir spectrum displayed the diagnostic absorption bands at 1720 and 1665 cm^{-1} for the ester carbonyl and the α,β-unsaturated ketone respectively. An exact mass measurement of the parent ion peak at 276.1732 in the mass spectrum further confirmed the gross structural assignment. Although by no means conclusive, the foregoing results were encouraging. Unfortunately, for reasons yet to be determined, the alkylation of the mixture of 25 and 26 with ethyl vinyl ketone was not reproducible. In spite of numerous attempts, with or without modifications, starting material was recovered intact.

The third approach which is currently being studied requires first the conversion of 25 into a compound of type 51. The latter is expected to undergo cyclization via an intramolecular alkylation process to complete the framework of capnellane (1). Although the feasibility of such a scheme remains to be seen, present results are promising. Treatment of a mixture of 25 and 26 with 1-bromo-3-methyl-2-butene[31] and sodium hydride in 1,2-dimethoxyethane resulted in the formation of two isomeric products, 52 and 53, in a ratio of about 3 : 1 and in a total yield of 84%. The major product 52 was readily separated from 53 by column chromatography and showed in the nmr spectrum two singlets at τ 8.38 and 8.27 for the two methyl groups and a triplet at τ 4.96 for the vinylic proton. The ir spectrum displayed the ester and the ketone absorption bands at 1725 and 1745 cm^{-1} respectively. The nmr and ir spectra of 53 were found to be similar to those of 52 and the isomeric relationship of these two compounds was further verified by their mass spectra which displayed

in each case a molecular ion peak at 368.1481. The location of the ester group and thus that of the ketone of these two products however could not be deduced unambiguously on the basis of the available spectral data. The assignments* were made as a logical extension of the detected composition of the starting mixture. Furthermore, the alkylation, in each case, was expected to proceed with a normal stereochemical course with the reagent entering from the less hindered convex face[32]. Consequently, the newly introduced side chain, in both products, was assigned cis to the ring juncture hydrogen atoms.

Prior to establishing proper functionalities for cyclization of 52, its ester group was first converted to a methyl group as follows. Reduction of 52 with lithium aluminum hydride afforded a 75% yield of the corresponding diol 54 whose ir spectrum showed hydroxyl bands at 3620, 3540 and 3420 cm^{-1}, and the absence of any carbonyl absorptions. The nmr spectrum displayed no signals for the ester grouping. A molecular ion peak at 328.1530 further confirmed the assigned structure. Moffatt oxidation[33] of diol 54 with dicyclohexylcarbodiimide and dimethyl sulfoxide in the presence of trifluoroacetic acid and pyridine in benzene gave rise to keto aldehyde 55 in quantitative yield. The ir spectrum showed, in addition to the cyclopentanone absorption at 1735 cm^{-1}, the diagnostic aldehyde bands at 2820, 2710 and 1710 cm^{-1}. In the nmr spectrum the aldehydic proton

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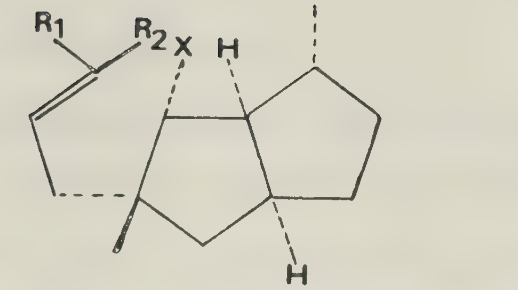
*The structure of 40 was further confirmed during the subsequent transformations.

appeared at τ 0.51 as a singlet. A molecular ion peak at 324.1214 was in accord with the formula of $C_{17}H_{24}O_2S_2$.

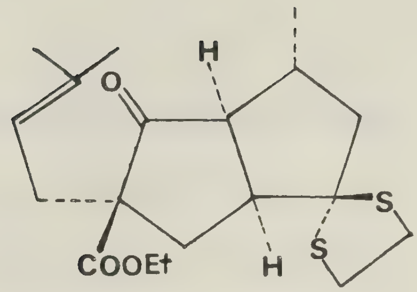
In principle, the conversion of the aldehyde group of 55 to a methyl could be carried out by several different methods. It was preferred to proceed the transformation via a thioketal intermediate so that its subsequent desulfurization could result in concomitant removal of the pre-existing thioketal group. Selective thioketalization of 55 was effected by its treatment with 1,2-ethanedithiol and boron trifluoride etherate at 0°C for a short period. The dithioketal 56 thus obtained in 70% yield showed in the nmr spectrum two thioketal singlets at τ 6.86 and 6.76 each integrated for four protons and another singlet at τ 5.20 for the hydrogen atom adjacent to the thioketal moiety. Its ir spectrum showed a band at 1735 cm^{-1} for the ketone carbonyl and the complete absence of aldehydic signals. A molecular ion peak corresponding to a molecular formula of $C_{19}H_{28}OS_4$ was observed in its mass spectrum.

Subsequently, dithioketal 56 was subjected to desulfurization with W-2 Raney nickel in benzene. Under these conditions, 56 afforded, in addition to a 43% yield of the desirable product 57, an over-reduced product 58 in 10% yield. In the nmr spectra, both 57 and 58 showed the absence of thioketal signals. Ketone 58 further showed the absence of a triplet expected for a vinylic proton and a doublet at τ 9.08 for the six *gem*-dimethyl hydrogen atoms indicating the saturation of the double bond. The structures were further defined by their mass spectra which displayed molecular ion peaks at 220.1829 and 222.1976 for 57

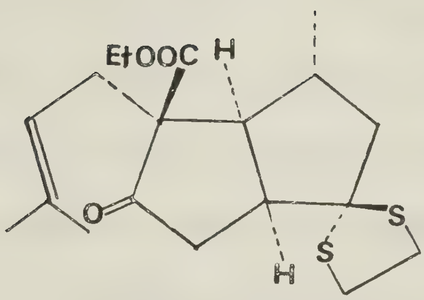


51 X = LEAVING GROUP

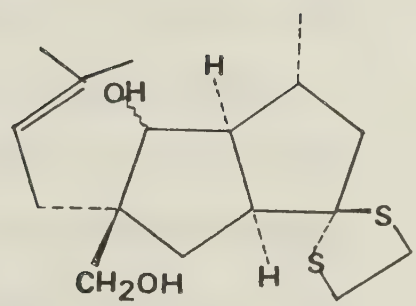
R_1 , R_2 = CHO , CH_3



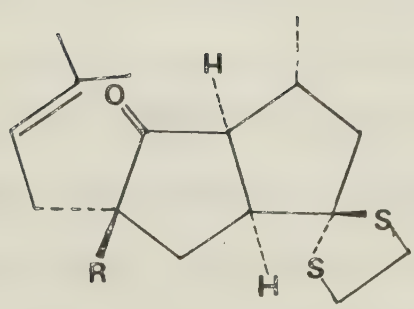
52



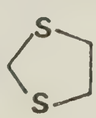
53

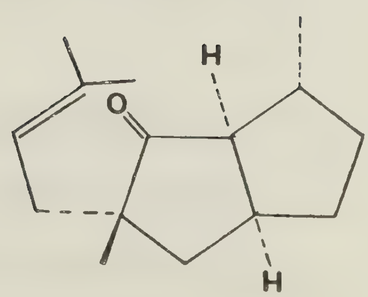


54



55 R = CHO

56 R = CH 



57

and 58, respectively.

Enone 57 contains the required carbon skeleton of the target molecule 1 with the exception of a missing C_1-C_{11} linkage. The formation of such a bond could be conceivably achieved, as discussed previously, via an intramolecular alkylation process involving the intermediacy of compound 59. Towards this end, 57 was reduced with lithium aluminum hydride in ether at 0°C and a 94% yield of a mixture of two epimeric alcohols in ca. 4 : 1 ratio was obtained. Since the hydride ion was expected to add preferentially from the sterically less hindered side, the stereochemistry of the major and minor isomers could be readily assigned as shown in 59 and 59a respectively. These assignments were substantiated by the fact that, in case of major isomer, the proton adjacent to the hydroxyl group appeared in the nmr spectrum at an abnormally high field of τ 6.77 as a doublet*. This observation could be readily attributed to the shielding effect of the double bond and required the proton to be cis to the side chain. Alcohol 59 could be converted to the corresponding tosylate 60 upon treatment with p-toluenesulfonyl chloride in pyridine. The attempted oxidation of the latter compound with

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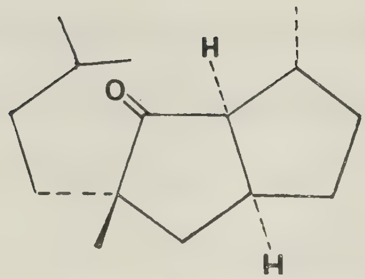
*The fact that both this proton and the corresponding one of the minor isomer 59a appeared as a doublet in nmr spectra further substantiated the structural assignment of their precursor 52. Should the epimeric alcohols be derived from 53, more complex splitting pattern, i.e., a triplet or a doublet of doublets would be expected for each of them.

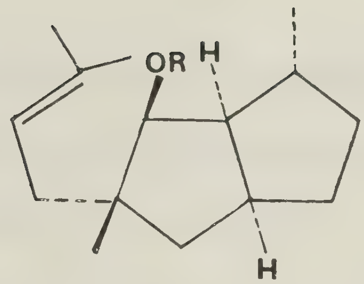
selenium dioxide in order to incorporate the required aldehyde group was however unsuccessful due to the instability of its p-toluenesulfonyl group.

Consequently, 59 was first converted to acetate 61 using acetic anhydride in pyridine. Selenium dioxide oxidation[34] of 61 proceeded smoothly to give an 81% yield of aldehyde 62 whose structure was evident from the following spectral data. The ir spectrum displayed, in addition to the characteristic α,β-unsaturated aldehyde bands at 2820, 2720 and 1690 cm^{-1}, the ester and the double bond absorption bands at 1740 and 1645 cm^{-1} respectively. Its molecular composition of $C_{17}H_{26}O_3$ was indicated by the mass spectrum exhibiting a parent ion peak at 278.1869. The nmr spectrum was also in agreement with the assigned structure showing an aldehydic singlet at τ 0.65, a triplet at τ 3.56 for the vinylic proton and three singlets at τ 8.0, 8.24, and 9.01 and a doublet at τ 9.10 for a total of four methyl groups. With respect to the stereochemistry of its double bond, the *trans* assignment was made on the basis of ample precedents which showed that the selenium dioxide oxidation of isopropylidene derivatives resulted in predominantly or exclusively the *trans* isomers[34,35].

The preparation of 62 in a highly stereoselective manner represents the present state of our studies towards the total synthesis of Capnellane 1. To complete the synthesis from 62, it requires, by and large, three major operations : the conversion of the acetoxy group to a suitable leaving group with retention of configuration, cyclization by an intramolecular alkylation, and the removal of the remaining functional groups.



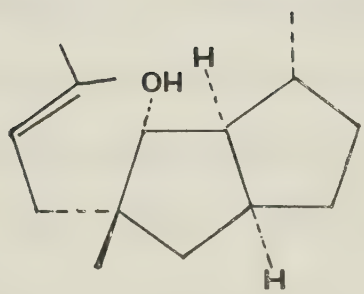
58



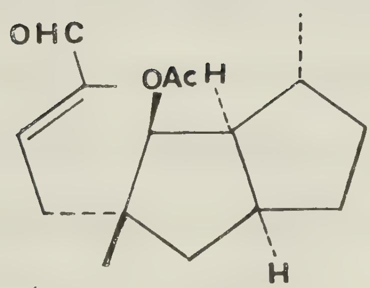
59 R = H

60 R = $SO_2C_6H_4CH_3$

61 R = $COCH_3$



59a



62

EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were performed by the microanalytical laboratory of this department. Ir spectra were recorded on a Perkin-Elmer Models 337 or 457 spectrophotometers. Nmr spectra were recorded on Varian A-60, HR-100, and 90 MHz Perkin-Elmer 32 spectrometers using tetramethylsilane as internal standard. Mass spectra were recorded on A.E.I. Model MS-2, MS-9 or MS-50 mass spectrometers. Gas chromatographic (gc) analyses were performed using a Hewlett-Packard research chromatograph Model 5750 with a column of 15% SE 30 Chromosorb W, 80-100 mesh. Solutions were dried over anhydrous magnesium sulfate unless otherwise specified.

Material

Dimethyl sulfoxide (DMSO) was freshly distilled from calcium hydride. Acetone was dried over calcium sulfate for 14 hr and distilled from potassium permanganate. 1,2-Dimethoxyethane (DME) was freshly distilled from lithium aluminum hydride. 2-Cyclopenten-1-one was prepared from a mixture of 3,4- and 3,5-cyclopentenediol (Research Organic/Inorganic Chemical Corp.) according to the procedure of DePuy and Eliers[17-19]. Bromoacetone was prepared from acetone according to the reported procedure[30]. 1-Bromo-3-methyl-2-butene was prepared from 2-methyl-3-buten-2-ol (97%; Aldrich Chemical Company) according to the reported

procedure of Crombie *et al.*[31]. Silica gel, 0.15-0.33 mm granulation, was used as absorbant for column chromatography.

4-Acetoxy-2-cyclopenten-1-one

This compound was prepared from 2-cyclopenten-1-one using the procedure of DePuy *et al.*[18] with modifications. A mixture of 2-cyclopenten-1-one (53 g, 0.65 mol), N-bromosuccinimide (98% purity; 116.6 g, 0.65 mol) and 2,2'-azobis(2-methylpropionitrile) (2.75 g) in 800 ml of carbon tetrachloride was heated on a steam bath for 1 hr. The mixture was cooled to 0°C, filtered, and the residue washed thoroughly with ice-cold carbon tetrachloride. The filtrate was washed with 1 N sodium thiosulfate (2 X 200 ml) and water (200 ml), dried, filtered and concentrated to give crude 4-bromo-2-cyclopenten-1-one as an oil. This oily product (105 g, *ca.* 0.63 mol) without purification was dissolved in 1000 ml of glacial acetic acid and silver acetate (122 g, 0.73 mol) was added. After heating under a nitrogen atmosphere at reflux for 24 hr, the resulting mixture was filtered and the residue washed with glacial acetic acid. Removal of the solvent *in vacuo* followed by distillation of the remaining oil at 57-58°C/2 mm yielded 45 g (50%) of 4-acetoxy-2-cyclopenten-1-one as a colorless oil : ir (film) 1743 (ester), 1730 (ketone) and 1593 cm^{-1} (double bond); nmr (CCl_4) τ 7.96 (s, 3 H, CH_3CO-), 7.75 (dd, 1 H, J = 19 Hz, J' = 6 Hz, -C$\underline{H}$(H)CO-), 7.29 (dd, 1 H, J = 19 Hz, J' = 3 Hz, -C$\underline{H}$(H)CO-), 4.24 (dddd, 1 H, J = 6 Hz, J' = 3 Hz, J" = 2 Hz, J"' = 1 Hz, -C$\underline{H}$OCOCH_3), 3.77 (dd, 1 H, J = 6 Hz, J' = 1 Hz, -COC$\underline{H}$=) and 2.48 (dd, 1 H, J = 6 Hz, J' = 2 Hz, -C$\underline{H}$=CHCO-); mass spectrum M^+ 140.0476 (Calcd. for $C_7H_8O_3$: 140.0474).

4,6-Diacetoxybicyclo[3.2.0]heptan-2-one (13)

The apparatus used for the photocycloaddition reaction is shown in Figure I. A solution of vinyl acetate (650 ml, 6.8 mol) and 4-acetoxy-2-cyclopenten-1-one (45 g, 0.32 mol) in 650 ml of benzene was irradiated with a high-pressure quartz mercury-vapor lamp (450 W, Hanovia) using a pyrex filter at 0°C for 8 hr and at room temperature for 12 hr. During the irradiation a constant stream of dry and oxygen free nitrogen was passed through the solution to facilitate its mixing. Concentration of the reaction mixture under reduced pressure furnished 75 g of crude 13 as an oil.

6-Acetoxybicyclo[3.2.0]hept-3-en-2-one (14)

The crude photoadduct 13 (75 g) and p-toluenesulfonic acid monohydrate (3.2 g) were dissolved in 600 ml of benzene. The solution was stirred at room temperature under a nitrogen atmosphere for 24 hr. The reaction mixture was made basic with ice-cold saturated aqueous sodium carbonate solution. The benzene solution was seperated and the aqueous layer extracted with ether (4 X 200 ml). The organic solutions were washed with saturated aqueous sodium bicarbonate (300 ml) and water (300 ml), combined, dried, filtered, and concentrated to give a brown oil which was distilled at 85 - 87°C/0.5 mm giving 39.35 g (74% from 4-acetoxy-2-cyclopenten-1-one) of an epimeric mixture of 14: ir (film) 1735 (ester), 1704 (ketone) and 1573 cm^{-1} (double bond); The mixture showed the following two sets of signals in its nmr spectrum (CCl_4) :

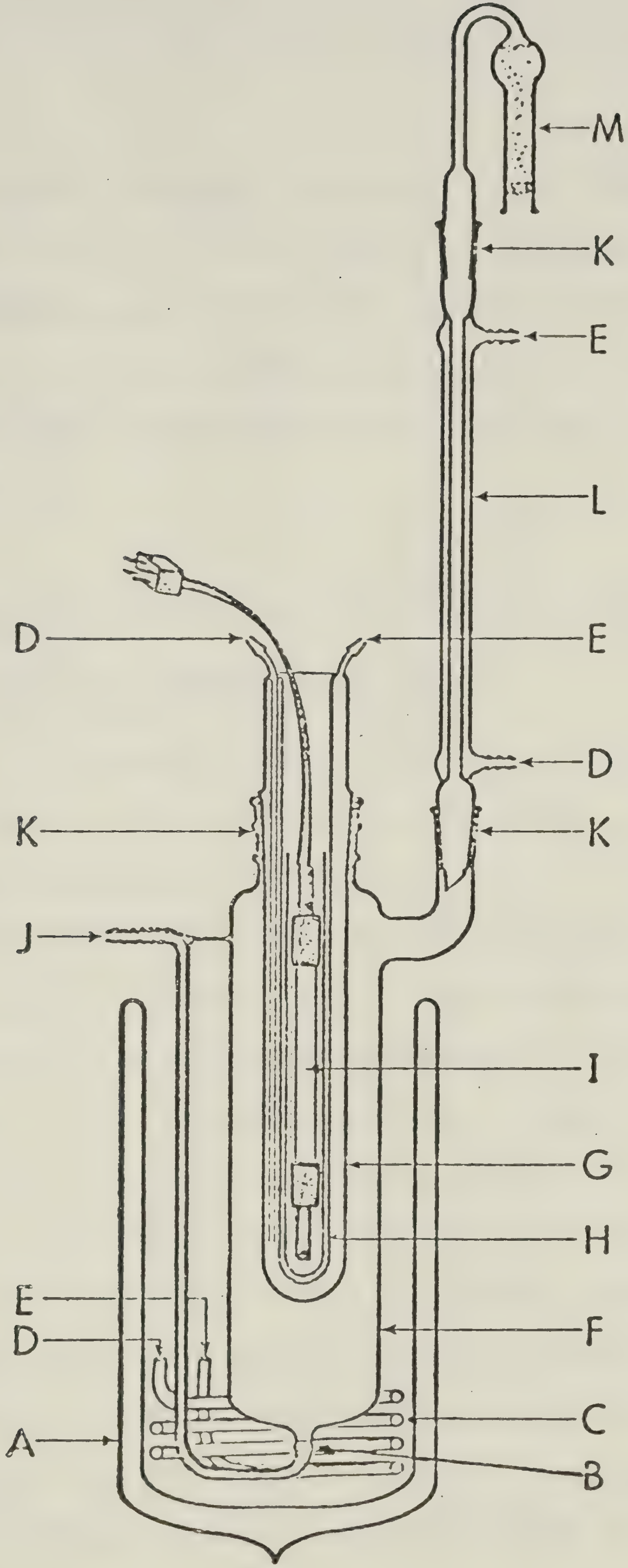


Fig. 1. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

τ 8.0 (s, 3 H, CH_3COO-), 4.82 (td, 1 H, J = J' = 8 Hz, -$\overset{|}{C}$HO-), 3.65 (ddd, 1 H, J = J' = 6 Hz, J" = 1 Hz, =CHCO-), and 2.24 (dd, 1 H, J = 6 Hz, J' = 3 Hz, -C<u>H</u>=CHCO-), and τ 7.94 (s, 3 H, CH_3COO-), 5.50 (m, 1 H, -$\overset{|}{C}$HO-), 3.72 (dd, 1 H, J = J' = 6 Hz, =CHCO-), 2.54 (dd, 1 H, J = 6 Hz, J' = 3 Hz, -C<u>H</u>=CHCO-). The former and the latter set of singals were integrated to a ratio of <u>ca</u>. 10 : 7.

<u>6-Acetoxy-4-methylbicyclo[3.2.0]heptan-2-one (15) and 6-hydroxy-4-methyl-3-(1-oxoethyl)bicyclo[3.2.0]heptan-2-one (16)</u>

(A) At 0°C, to a vigorously stirred suspension of cuprous iodide (19.43 g, 0.102 mol) in 150 ml of anhydrous ether under a nitrogen atmosphere, was added dropwise over a period of 40 min, 125 ml (0.2 mol) of 1.6 M methyllithium in ether. After stirring for an additional 20 min, a solution of <u>14</u> (5.19 g, 0.031 mol) in 60 ml of ether was added dropwise over a 40 min period. The reaction was maintained at 0°C with stirring for an additional 1.5 hr. The resulting mixture was added slowly to vigorously stirred ice-cold 2 N hydrochloric acid (300 ml) and filtered. The filtrate was extracted with chloroform (3 X 500 ml). The combined organic extracts were washed with water and saturated aqueous sodium chloride, dried, filtered and concentrated. The oily product was chromatographed over silica gel using a solution of 5% ether in benzene as eluent giving 2.73 g (50%) of <u>15</u> as a mixture of two epimers : ir (film) 1735 cm^{-1} (ketone and ester); nmr (CCl_4) τ 9.02, 8.98 (both d, total 3 H, J = 7 Hz each, CH_3-), 8.0 (s, 3 H, -$COCH_3$) and 5.04 (m, 1 H, -$\overset{|}{C}$HO-); mass spectrum M^+ 182.0945 (Calcd. for $C_{10}H_{14}O_3$: 182.0943).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.92 ; H, 7.74 . Found : C , 65.94 ; H , 7.81 .

Further elution with a solution of 10% ether in benzene afforded 1.18 g (21%) of 16 : ir (film) 3450 (alcohol), 1725 (broad, ketone) and 1640 cm^{-1} (conjugated ketone); nmr (CCl_4) τ 8.95 (d, 3 H, J = 7 Hz, CH_3-), 7.98 (s, 3 H, -$COCH_3$), 6.22 (broad s, 1 H, -OH) and 5.22 (m, 1 H, -CHOH); mass spectrum M^+ 182.0970 (Calcd. for $C_{10}H_{14}O_3$: 182.0943).

(B) To a cold (0°C) slurry of 24.5 g (129 mmol) of copper(I) iodide in 500 ml of ether under a nitrogen atmosphere, was added dropwise 100 ml of an ethereal solution containing 0.25 mol of methyl magnesium bromide. The resulting solution was stirred for 10 min and a solution of 14 (5 g, 30 mmol) in 120 ml of ether was added dropwise over a 15 min period. The reaction mixture after stirring for an additional 75 min was poured into ice-cold saturated aqueous ammonium chloride solution (800 ml). Ammonium hydroxide (6 N, 500 ml) was added to dissolve all the white precipitates formed. The organic layer was separated, combined with the ether extracts (3 X 500 ml) of the aqueous phase, dried and concentrated to give an oily product which was chromatographed on silica gel. Elution with a solution of 5% ether in benzene gave 2.80 g(51%) of 15. Further elution with a solution of 10% ether in benzene gave 982 mg (18%) of 16.

6-Acetoxy-4-methyl-3-(1-oxoethyl)bicyclo[3.2.0]heptan-2-one (18)

A solution of 16 (1.10 g, 6.04 mmol) and acetic anhydride (6 ml)

in pyridine (12 ml) was allowed to stand in dark at room temperature for 22 hr. The solution was concentrated and the residue chromatographed on silica gel. Elution with a solution of 5% ether in benzene gave 540 mg (40%) of 18 : ir (film) 3460 (enol), 1738 (ketone and ester), 1655 (conjugated ketone) and 1620 cm^{-1} (enol double bond); nmr (CCl_4) τ 8.95 (d, 3 H, J = 6 Hz, CH_3-), 8.03 (s, 3 H, $-COCH_3$), 8.0 (s, 3 H, $-OCOCH_3$) and 4.76 - 5.07 (m, 1 H, $-\overset{|}{C}HO-$); mass spectrum m/e (M-59) 165.0911 (Calcd. for $C_{10}H_{13}O_2$: 165.0915).

6-Hydroxy-4-methylbicyclo[3.2.0]heptan-2-one (20) and 3-carbmethoxy-2-(1-methyl-3-oxobutyl)cyclobutanol (21)

(A) From pure 15.

A mixture of 267 mg (1.46 mmol) of 15 and 3 ml of saturated aqueous sodium carbonate in 3 ml of methanol was stirred at room temperature for 3 hr. The resulting mixture was diluted with water (20 ml) and extracted with methylene chloride (4 X 20 ml). The organic solution was dried and concentrated. Chromatography of the residue over silica gel using a solution of 20% ether in benzene as eluent gave 130 mg (64%) of 20 : ir (film) 3430 (alcohol) and 1730 cm^{-1} (ketone); nmr (CCl_4) τ 9.02 (d, 3 H, J = 7 Hz, CH_3-), 5.89 (m, 1 H, $-\overset{|}{C}\underline{H}OH$) and 5.44 (s, 1 H, -OH); mass spectrum M^+ 140.0814 (Calcd. for $C_8H_{12}O_2$: 140.0837).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found : C, 68.44; H, 8.67.

(B) From the mixture of 15 and 16.

To a solution of crude mixture of 15 and 16 (from 14; 5.503 g, 33.16 mmol) in methanol (77 ml), was added 77 ml of saturated aqueous sodium

carbonate. The resulting mixture was stirred at room temperature for 3 hr and worked up in the same manner described above. Purification of the residue over silica gel using a solution of 20% ether in benzene afforded 726 mg (9% from 14) of 21 : ir (film) 3480 (alcohol) and 1715 cm^{-1} (broad, ketone and ester); nmr (CCl_4) τ 9.14 (d, 3 H, J = 6 Hz, CH_3-), 7.95 (s, 3 H, -$COCH_3$), 6.30 (s, 3 H, -$COOCH_3$) and 5.85 (broad s, 1 H, -OH); mass spectrum m/e (M - 17) 197. Further elution with the same solvent gave 1.37 g (33% from 14) of 20.

4-Methylbicyclo[3.2.0]heptan-6-ol (22)

To a stirred solution of 2.059 g (14.7 mmol) of 20 in 19.7 ml of triethylene glycol, was added 2.6 ml of 100% hydrazine hydrate. The mixture was heated at 110°C for 1 hr and, after cooling to room temperature, potassium hydroxide (2.63 g, 47 mmol) was added. The resulting mixture was heated at 150°C for 5 hr. After cooling to 0°C, it was poured into water (50 ml), acidified with 10 ml of concentrated hydrochloric acid, and extracted with chloroform (4 X 50 ml). The combined organic extracts were dried, filtered, and concentrated. Column chromatography of the yellow oil on silica gel using benzene as eluent yielded 873 mg (32%) of 22 : ir (film) 3300 cm^{-1} (alcohol); nmr (CCl_4) τ 9.21 (d, 3 H, J = 7 Hz, CH_3-), 6.32 (s, 1 H, -OH), 6.25 (m, 1 H, -$\overset{|}{C}\underline{H}OH$); mass spectrum M^+ 126.

4-Methylbicyclo[3.2.0]heptan-6-one (17)

At 0°C, to a solution of 485 mg (3.85 mmol) of alcohol 22 in 5 ml

of acetone, was added 8 N Jones reagent until the orange color remained (ca. 1.5 ml). The reaction mixture after stirring for an additional 5 min was poured into 50 ml of water. Extraction with methylene chloride (4 X 40 ml) followed by the usual work-up of the extracts gave an oil (430 mg). Bulb-to-bulb distillation of the oil at 55 - 60°C (oven temperature)/1mm yielded 290 mg (61%) of ketone 17 : ir (film) 1775 cm^{-1} (ketone).

2-Ethylenedithio-4-methylbicyclo[3.2.0]heptan-6-ols (23 and 23a)

At 0°C, to a solution of 2.718 g (19.4 mmol) of 20 in 9.4 ml (112.3 mmol) of 1,2-ethanedithiol, was added 0.94 ml of boron trifluoride etherate. The mixture after stirring under a nitrogen atmosphere for 3 hr was poured into ice-cold 4 N sodium hydroxide (100 ml) and extracted with methylene chloride (4 X 100 ml). The extracts were washed with 4 N sodium hydroxide (2 X 100 ml) and water. Drying, filtration and concentration gave an oil which was chromatographed over silica gel. Elution with a solution of 5% ether in benzene afforded 1.208 g (30%) of 23 : ir (film) 3345 cm^{-1} (alcohol); nmr (CCl_4) τ 8.87 (d, 3 H, J = 7 Hz, CH_3-), 6.82 (m, 4 H, -SCH_2CH_2S-), and 5.83 (m, 1 H, -CHOH); mass spectrum M^+ 216.0651 (Calcd. for $C_{10}H_{16}OS_2$: 216.0643).

Anal. Calcd. for $C_{10}H_{16}OS_2$: C, 55.48; H, 7.45; S, 29.62. Found : C, 55.56; H, 7.55; S, 29.78.

Further elution with the same solvent gave 2.574 g (64%) of 23a : ir (film) 3320 cm^{-1} (alcohol); nmr (CCl_4) τ 8.87 (d, 3 H, J = 7 Hz, CH_3-), 6.82 (m, 4 H, -SCH_2CH_2S-), 6.02 (s, 1 H, -OH) and 6.12 (m, 1 H, -CHOH); mass spectrum M^+ 216.0651 (Calcd. for $C_{10}H_{16}OS_2$: 216.0643).

2-Ethylenedithio-4-methylbicyclo[3.2.0]heptan-6-one (24)

(A) From the mixture of 23 and 23a.

To a cold (0°C) solution of 2.67 g (12.36 mmol) of 23 and 23a in 53.4 ml of DMSO, was added 33.4 ml of acetic anhydride. The reaction mixture was kept at ≈3°C for 6 days. Water (100 ml) was added and the resulting solution after stirring at room temperature for 4 hr was extracted with methylene chloride (4 X 100 ml). The extracts were washed with 2 N NaOH (2 X 100 ml), water (100 ml) and worked up in the usual manner. The product thus obtained was chromatographed on silica gel. Elution with benzene gave 2.25 g (85%) of 24 : ir (film) 1777 cm^{-1} (ketone); nmr (CCl_4) τ 8.81 (d, 3 H, J = 7 Hz, CH_3-) and 6.73 (m, 4 H, $-SCH_2CH_2S-$); mass spectrum M^+ 214.0485 (Calcd. for $C_{10}H_{14}OS_2$: 214.0484).

Anal. Calcd. for $C_{10}H_{14}OS_2$: C, 56.04; H, 6.58; S, 29.92. Found : C, 56.04; H, 6.58; S, 29.99.

(B) From 23a.

Treatment of 23a (2.0 g, 9.35 mmol) under the same reaction conditions gave 1.579 g (79%) of 24.

3-Carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]octan-2-one (25) and 2-carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]octan-3-one (26)

A solution of 24 (1.365 g, 6.38 mmol) in 30 ml of anhydrous ether under a nitrogen atmosphere was cooled to -35°C (dry ice - carbon tetrachloride) and boron trifluoride etherate (1.10 ml, 9.57 mmol) was slowly added. The resulting solution was stirred for 5 min. Ethyl diazo-acetate (1.2 ml, 9.57 mmol) was then added dropwise and stirring was

continued for 20 min. Saturated aqueous sodium bicarbonate (150 ml) was added. The resulting mixture after standing at room temperature for 15 min was extracted with methylene chloride (4 X 100 ml). The extracts were washed with 2 N hydrochloric acid (2 X 150 ml) and water (150 ml), dried, and filtered. The filtrate was concentrated and the residue chromatographed on silica gel using a solution of 3% ether in benzene as eluent giving 1.737 g (85%) of a mixture of 25 and 26. The mixture gave the following spectral data : ir (film) 3400 (enol), 1745 (ketone), 1718 (ester), 1650 (conjugated ester) and 1610 cm^{-1} (enol double bond); nmr (CCl_4) two sets of signals at τ 8.81 (d, 6 H, J = 6 Hz, CH_3-), 8.72 (t, 3 H, J = 7 Hz, -$CH_2C\underline{H}_3$), 6.81 (s, 4 H, -SCH_2CH_2S-) and 5.81 (q, 2 H, J = 7 Hz, -$OC\underline{H}_2CH_3$) and at τ 8.81 (d, 6 H, J = 6 Hz, CH_3-), 8.74 (t, 3 H, J = 7 Hz, -$CH_2C\underline{H}_3$), 6.74 (s, 4 H, -SCH_2CH_2-) and 5.87 (q, 2 H, J = 7 Hz, -$OC\underline{H}_2CH_3$); mass spectrum M^+ 300.08541 (Calcd. for $C_{14}H_{20}O_3S_2$: 300.08539).

Anal. Calcd. for $C_{14}H_{20}O_3S_2$: C, 55.97; H, 6.71. Found : C, 56.36; H, 6.74.

3-Carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]octan-2-ol (27) and 2-carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]octan-3-ol (28)

A mixture of 25 and 26 (270 mg, 0.9 mmol) was dissolved in 10 ml of 98% ethanol and sodium borohydride (135 mg, 3.55 mmol) was added in small portions at 0°C under a nitrogen atmosphere. The resulting solution was stirred for 10 min. Excess reagent was destroyed by slow addition of 20 ml of saturated ammonium chloride and 20 ml of 2 N HCl. The mixture was extracted with methylene chloride. The organic solutions were combined,

dried, and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 5% ether in benzene gave rise to 140 mg (51%) of 27 : ir (film) 3480 (alcohol) and 1724 cm^{-1} (ester). Further elution with the same solvent gave 35 mg (13%) of 28.

2-Acetoxy-3-carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]octane (29)

A solution of 140 mg (0.46 mmol) of 27 and 0.5 ml of acetic anhydride in 1 ml of pyridine was allowed to stand in dark at room temperature for 2 days. Pyridine and excess acetic anhydride were removed under aspirator pressure. The residue was purified by column chromatography over silica gel using a solution of 2% ether in benzene as eluent giving 140 mg (89%) of 29 : ir (film) 1735 cm^{-1} (esters); nmr (CCl_4) τ 9.02 (d, 3 H, J = 6 Hz, CH_3-), 8.76 (t, 3 H, J = 7 Hz, $-CH_2C\underline{H}_3$), 8.07 (s, 3 H, $-COCH_3$), 6.77 (s, 4 H, $-SCH_2SCH_2S-$), 5.93 (q, 2 H, J = 7 Hz, $-OC\underline{H}_2CH_3$) and 4.71 (dd, 1 H, J = 9 Hz, J' = 8 Hz, -CHO-); mass spectrum M^+ 344.11163 (Calcd. for $C_{16}H_{24}O_4S_2$: 344.11160).

3-Acetoxy-2-carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]octane (30)

Under the same reaction conditions described for the transformation of 27 → 29, alcohol 28 (35 mg, 0.116 mmol) was acetylated. Purification of the crude product by column chromatography using a solution of 2% ether in benzene as eluent yielded 35 mg (88%) of 30 : ir (film) 1735 cm^{-1} (esters); nmr (CCl_4) τ 8.93 (s, 3 H, J = 5 Hz, CH_3-), 8.86 (t, 3 H, J = 7 Hz, $-CH_2C\underline{H}_3$), 8.01 (s, 3 H, $-COCH_3$), 6.90 (s, 4 H, $-SCH_2CH_2S-$), 5.91 (q, 2 H, J = 7 Hz, $-OC\underline{H}_2CH_3$), 5.72 (td, 1 H, J = 7 Hz, J' = 9 Hz, -CHO-); mass spectrum

M^{+} 344.11115 (Calcd. for $C_{16}H_{24}O_4S_2$: 344.11160).

3-Carbethoxy-6-ethylenedithio -8-methylbicyclo[3.3.0]oct-2-ene (31).

To a solution of 140 mg (0.41 mmol) of 29 in 2.5 ml of DME under a nitrogen atmosphere, were added 35 mg (0.83 mmol) of sodium hydride (57%) and 2 drops (ca. 20 mg) of t-amyl alcohol. The reaction mixture after stirring at 40 - 50°C overnight, was cooled to room temperature, poured into water(10 ml) and extracted with methylene chloride. The organic extracts were washed with 1 N sodium hydroxide (2 X 40 ml) and water (40 ml), and worked up in the usual manner. The residue was chromatographed on silica gel with benzene elution giving 45 mg(39%) of 31 : ir (film) 1715 (ester) and 1618 cm^{-1} (double bond); nmr (CCl_4) τ 8.83 (d, 3 H, J = 6 Hz, $-CH_3$), 8.7 (t, 3 H, J = 6 Hz, $-CH_2C\underline{H_3}$), 6.79 (s, 4 H, $-SCH_2CH_2S-$), 5.86 (q, 2 H, J = 7 Hz, $-C\underline{H_2}CH_3$) and 3.49 (td (?), 1 H, J = J' = 2 Hz, -CH=); mass spectrum M^{+} 284.09071 (Calcd. for $C_{14}H_{20}O_2S_2$: 284.09048).

2-Carbethoxy-6-ethylenedithio-8-methylbicyclo[3.3.0]oct-2-ene (32)

By the same procedure described in the above experiment, 32 was prepared from 30 (30 mg, 0.088 mmol), DME(0.8 ml), sodium hydride (57%; 8 mg, 0.19 mmol) and 2 drops (ca. 20 mg) of t-amyl alcohol. Pure 32 (15 mg; 60%) showed the following spectral data : ir (film) 1718 (ester) and 1625 cm^{-1} (double bond); nmr (CCl_4) τ 8.74 (d, 3 H, J = 5 Hz, CH_3-), 8.71 (t, 3 H, J = 6 Hz, $-CH_2C\underline{H_3}$), 6.82 (s, 4 H, $-SCH_2CH_2S-$), 5.88 (q, 2 H, J = 7 Hz, $-C\underline{H_2}CH_3$) and 3.49(td (?), 1 H, J = J' = 2 Hz, -CH=); mass spectrum M^{+} 284.09020 (Calcd. for $C_{14}H_{20}O_2S_2$: 284.09048).

<u>3-Carbethoxy-6-ethylenedithio-8-methyl-3-(2-oxopropyl)bicyclo[3.3.0]octan-2-one (36) and 2-carbethoxy-6-ethylenedithio-8-methyl-2-(2-oxopropyl)bicyclo-[3.3.0]octan-3-one (37)</u>

At 0°C, to a suspension of 95 mg (2.256 mmol) of sodium hydride (57%) in 10 ml of DME under a nitrogen atmosphere, was added dropwise a solution of 616 mg (2.053 mmol) of 25 and 26 in 5 ml of DME. The reaction mixture was stirred at room temperature for 10 min and bromoacetone (463 mg, 3.380 mmol) was added. Stirring was continued for 10 hr and 20 ml of water was slowly added. Acidification with 2 N hydrochloric acid followed by extraction with methylene chloride (4 X 30 ml) and the usual work-up of the extracts gave 1.20 g of a yellow oil which was chromatographed on silica gel. Elution with a solution of 1% ether in benzene gave 581 mg (79%) of a mixture of 36 and 37 : ir (film) 1745 (five-membered ketone) and 1720 cm^{-1} (ester and ketone); nmr (CCl_4) τ 8.52 - 9.03 (complex, total 6 H, $-CH_3$ and $-OCH_2C\underline{H}_3$), 8.0, 7.92 (both s, total 3 H, $-COCH_3$), 6.79, 6.75 (both s, total 4 H, $-SCH_2CH_2S-$), 5.91 (q, 2 H, J = 7 Hz, $-C\underline{H}_2CH_3$); mass spectrum M^+ 356.11119 (Calcd. for $C_{17}H_{24}O_4S_2$: 356.11180).

<u>3-Carbethoxy-3-(2-ethylenedioxypropyl)-6-ethylenedithio-8-methylbicyclo-[3.3.0]octan-2-one (40) and 2-carbethoxy-2-(2-ethylenedioxypropyl)-6-ethylenedithio-8-methylbicyclo[3.3.0]octan-3-one (41)</u>

A mixture of 36 and 37 (424 mg, 1.191 mmol) was dissolved in 50 ml of benzene. Ethylene glycol (8 ml, 0.143 mol) and p-toluenesulfonic acid (40 mg, 0.232 mmol) were added. The resulting solution was refluxed

with a Dean-Stark water separator under a nitrogen atmosphere for 20 hr. Benzene was partially (ca. 15 ml) removed by distillation and the remaining mixture after cooling to room temperature was poured into 30 ml of saturated aqueous sodium bicarbonate and extracted with methylene chloride (4 X 20 ml). The combined organic fractions were dried, filtered and concentrated. The crude oil was chromatographed on silica gel using a solution of 5% ether in benzene as eluent giving 462 mg (97%) of a mixture of 40 and 41 : ir (film) 1742 (ketone) and 1720 cm^{-1} (ester); nmr (CCl_4) τ 8.80 (broad s, total 9 H, 3 CH_3-), 6.86, 6.79 (both s, total 4 H, -SCH_2CH_2S-), 6.20 (s, 4 H, -OCH_2CH_2O-) and 5.93 (q, 2 H, J = 7 Hz, -$C\underline{H}_2CH_3$); mass spectrum M^+ 400.1382 (Calcd. for $C_{19}H_{28}O_5S_2$: 400.1385).

<u>3-(Carbethoxy-6-ethylenedithio-8-methyl-3-(3-oxopentyl)bicyclo[3.3.0]-octan-2-one (45) and 2-carbethoxy-6-ethylenedithio-8-methyl-2-(3-oxo-pentyl)bicyclo[3.3.0]octan-3-one (46)</u>

To a cold (0°C) solution of 493 mg (1.643 mmol) of 25 and 26 in 20 ml of DME under a nitrogen atmosphere were added sodium hydride (57%; 84 mg, 1.995 mmol), t-amyl alcohol (176 mg, 2.00 mmol) and ethyl vinyl ketone (350 mg, 4.167 mmol). The reaction mixture was stirred for 6 hr. Water (30 ml) was added and the resulting mixture was acidified with 2 N hydrochloric acid and extracted with methylene chloride (4 X 30 ml). The combined methylene chloride solutions were worked up in the usual manner and the crude product chromatographed over silica gel using a solution of 2% ether in benzene as eluent giving , in addition to 100 mg (23%) of unreacted starting material, 212 mg (42% based on the

consumed material) of 45 and 46 : ir (film) 1742 (five-membered ketone) and 1710 cm^{-1} (ketone and ester); nmr (CCl_4) τ 9.04, 9.0 (both d, total 3 H, J = 6 Hz, $-CH_3$), 8.87 (t, 3 H, J = 7 Hz, $-CH_2\underline{CH_3}$), 8.75 (t, 3 H, J = 7 Hz, $-OCH_2\underline{CH_3}$), 6.72 (complex, 4 H, $-SCH_2CH_2S-$) and 5.88 (q, 2 H, J = 7 Hz, $-O\underline{CH_2}CH_3$); mass spectrum M^+ 384.1433 (Calcd. for $C_{19}H_{28}O_4S_2$: 384.1437).

3-Carbethoxy-8-methyl-3-(3-oxopentyl)bicyclo[3.3.0]octan-2-one (47) and/or 2-carbethoxy-8-methyl-2-(3-oxopentyl)bicyclo[3.3.0]octan-3-one (48)

To a stirred solution of 45 and 46 (160 mg, 0.417 mmol) in 2 ml of benzene, was added a suspension of 2.5 ml of W-4 Raney nickel in 10 ml of benzene. The mixture was stirred at room temperature for 20 hr and filtered. The residue was washed with benzene. The filtrate was concentrated to give 120 mg of crude oil which was dissolved in 2 ml of acetone. To this solution at 0°C, was added 8 N Jones reagent until the orange color was retained (ca. 0.7 ml) The reaction mixture was stirred for 30 min, diluted with 30 ml of water, and extracted with methylene chloride (4 X 30 ml). The organic solution was dried, filtered and concentrated. Column chromatography of the residue on neutral alumina (grade II) using Skelly B as eluent gave 30 mg (24%) of 47 and/or 48 : ir (film) 1740 (five-membered ketone) and 1710 cm^{-1} (ketone and ester); nmr (CCl_4) τ 9.03 (d, 3 H, J = 8 Hz, $-CH_3$), 8.85 (t, 3 H, J = 7 Hz, $-CH_2\underline{CH_3}$), 8.73 (t, 3 H, J = 7 Hz, $-OCH_2\underline{CH_3}$) and 5.87 (q, 2 H, J = 7 Hz, $-O\underline{CH_2}CH_3$); mass spectrum M^+ 284.18298 (Calcd. for $C_{17}H_{26}O_4$: 294.18311).

7-Carbethoxy-3,12-dimethyltricyclo[7.3.0.$0^{2,7}$]dodec-2-en-4-one (49) and/or 2-carbethoxy-6,12-dimethyltricyclo[7.3.0.$0^{2,7}$]dodec-6-en-5-one (50)

A solution of p-toluenesulfonic acid (35 mg, 0.204 mmol) in 15 ml of benzene was refluxed with a Dean-Stark water separator under a nitrogen atmosphere for an hour. Benzene (*ca.* 10 ml) was partially removed by distillation and another portion (10 ml) of benzene was added. The solution was further refluxed for 1 hr and 10 ml of benzene was distilled off. To the remaining solution, was added a solution of 47 and/or 48 (30 mg, 0.102 mmol) in 10 ml of benzene. The reaction mixture was refluxed for 24 hr and cooled to room temperature. Saturated aqueous sodium bicarbonate solution (15 ml) was added and the resulting mixture was extracted with methylene chloride (3 X 15 ml). The organic solution was dried, filtered and concentrated to give an oil which was chromatographed on silica gel. Elution with a solution of 2% ether in benzene yielded 12 mg (43%) of 49 and/or 50 : ir (film) 1720 (ester) and 1665 cm^{-1} (ketone); nmr (CCl_4) τ 8.83 (d, 3 H, J = 6 Hz, $-CH_3$), 8.73 (t, 3 H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 8.18 (s, 1 H, $CH_3C=$), and 5.86 (q, 2 H, J = 7 Hz, $-C\underline{H}_2CH_3$); mass spectrum M^+ 276.1732 (Calcd. for $C_{17}H_{24}O_3$: 276.1739).

3-Carbethoxy-6-ethylenedithio-8-methyl-3-(3-methyl-2-butenyl)bicyclo[3.3.0]-octan-2-one (52) and 2-carbethoxy-6-ethylenedithio-8-methyl-2-(3-methyl-2-butenyl)bicyclo[3.3.0]octan-2-one (53)

A mixture of 25 and 26 (834 mg, 2.78 mmol) was dissolved in 25 ml of DME at 0°C under a nitrogen atmosphere. Sodium hydride (57%; 128.5 mg,

3.058 mmol) was added. After the elution of hydrogen stopped, 0.48 ml (4.17 mmol) of 1-bromo-3-methyl-2-butene was added. The resulting mixture was stirred at room temperature for 30 min. Excess soduim hydride was destroyed by addition of water. The resulting mixture was acidified with 2 N hydrochloric acid and extracted with methylene chloride. The usual work-up of the extracts gave an oil (1.2 g). Column chromatography of the oil over silica gel using a solution of 20% n-pentane in benzene as eluent gave 632 mg (62%) of 52 : ir (film) 1745 (ketone) and 1725 cm^{-1} (ester); nmr (CCl_4) τ 8.77 (d, 3 H, J = 6 Hz, $-CH_3$), 8.76 (t, 3 H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 8.38, 8.27 (both s, 3 H each, $(CH_3)_2C=$), 6.74 (s, 4 H, $-SCH_2CH_2S-$), 5.89 (q, 2 H, J = 7 Hz, $-COOCH_2-$) and 4.96 (t, 1 H, J = 7 Hz, =CH-); mass spectrum M^+ 368.1481 (Calcd. for $C_{19}H_{28}O_3S_2$: 368.1483). Further elution with the same solvent afforded 226 mg (22%) of 53: ir (film) 1745 (ketone) and 1725 cm^{-1} (ester); nmr (CCl_4) τ 8.96 (d, 2 H, J = 6 Hz, $-CH_3$), 8.73 (t, 3 H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 8.38, 8.29 (both s, 3 H each, $(CH_3)_2C=$), 6.78 (s, 4 H, $-SCH_2CH_2S-$), 5.87 (q, 2 H, J = 7 Hz, $-COOCH_2-$), and 5.02 (t, 1 H, J = 8 Hz, =CH-); mass spectrum M^+368.1481 (Calcd. for $C_{19}H_{28}O_3S_2$: 368.1483).

Anal. Calcd. for $C_{19}H_{28}O_3S_2$: C, 61.92; H, 7.65. Found : C, 61.76; H, 7.59.

6-Ethylenedithio-3-hydroxymethyl-8-methyl-3-(3-methyl-2-butenyl)bicyclo-[3.3.0]octan-2-ol (54)

To a cold (0°C) solution of 52 (792 mg, 2.15 mmol) in 50 ml of ether, was added lithium aluminum hydride (123 mg, 3.23 mmol). The resulting

mixture after stirring for 20 hr was cooled to 0°C. Water and saturated ammonium chloride were added. The mixture was extracted with methylene chloride (4 X 40 ml) and the extracts were washed with saturated sodium chloride solution. Work-up of the organic solution in the usual manner gave a solid which was recrystalized from cyclohexane to give 532 mg (75%) of 54 : m.p. 113-114°C; ir (CCl_4) 3620, 3540 and 3420 cm^{-1} (alcohols) ; nmr (CCl_4) τ 8.87 (d, 3 H, J = 5 Hz, $-CH_3$), 8.27, 8.25 (both s, 3 H each, $(CH_3)_2C=$), 6.84 (s, 4 H, $-SCH_2CH_2S-$) and 4.8 (t, 1 H, J = 6 Hz, -CH=); mass spectrum M^+ 328.1530 (Calcd. for $C_{17}H_{28}O_2S_2$: 328.1530).

Anal. Calcd. for $C_{17}H_{28}O_2S_2$: C, 62.15; H, 8.59; S, 19.52. Found : C, 61.89; H, 8.57; S, 19.64.

6-Ethylenedithio-3-formyl-8-methyl-3-(3-methyl-2-butenyl)bicyclo[3.3.0]-octan-2-one (55)

To a solution of 54 (470 mg, 1.433 mmol) in 10 ml of anhydrous benzene and 100 ml of DMSO, were added sequentially 0.23 ml (2.866 mmol) of anhydrous pyridine, 0.12 ml (1.433 mmol) of trifluoroacetic acid, and 1.77 g (8.598 mmol) of dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 19 hr. Benzene (35 ml) was added and the crystalline N,N'-dicyclohexylurea was removed by filtration. The filtrate was washed with 2 N hydrochloric acid (2 X 40 ml), 2 N sodium hydroxide (2 X 40 ml) and water (40 ml). The aqueous solutions were extracted with benzene. The organic solutions were combined, dried, filtered, and evaporated to dryness under reduced pressure. The residue still contained a small amount of N,N'-dicyclohexylurea which was filtered off and washed

with Skelly B. The crude product was purified by column chromatography using 50% n-pentane in benzene as eluent to give 468 mg (~100%) of 55 : ir (film) 1735 (ketone) and 2820, 2710 and 1710 cm^{-1} (aldehyde); nmr (CCl_4) τ 8.81 (d, 3 H, J = 6 Hz, $-CH_3$), 8.39, 8.27 (both s, 3 H each, $(CH_3)_2C=$), 6.71-6.96 (m, 4 H, $-SCH_2CH_2S-$), 5.04 (t, 1 H, J = 7 Hz, -CH=) and 0.51 (s, 1 H, -CHO); mass spectrum M^+ 324.1214 (Calcd. for $C_{17}H_{24}O_2S_2$: 324.1210).

6-Ethylenedithio-3-ethylenedithiomethyl-8-methyl-3-(3-methyl-2-butenyl)-bicyclo[3.3.0]octan-2-one (56)

To a cold (0°C) solution of 55 (488 mg, 1.506 mmol) in 10 ml of methylene chloride and 0.25 ml (3.012 mmol) of 1,2-ethanedithiol was added boron trifluoride (10 drops; ca. 100 mg). After stirring at 0°C for 35 min (reaction monitored by tlc), the reaction mixture was poured into ice-cold 4 N sodium hydroxide (50 ml) and extracted with methylene chloride (4 X 30 ml). The extracts were washed with 4 N sodium hydroxide (2 X 50 ml) and water (50 ml). Drying, filtration, and concentration gave an oily product which was purified by column chromatography over silica gel using a solution of 50% n-pentane in benzene as eluent to give 423 mg (70%) of 56 : ir (film) 1735 cm^{-1} (ketone); nmr (CCl_4) τ 8.74 (d, 3 H, J = 6 Hz, $-CH_3$), 8.40, 8.27 (both s, 3 H each, $(CH_3)_2C=$), 6.86, 6.76 (both s, 4 H each, $-SCH_2CH_2S-$), 5.20 (s, 1 H, -SCHS-) and 4.96 (t, 1 H, J = 7 Hz, =CH-); mass spectrum M^+ 400.1036 (Calcd for $C_{19}H_{28}OS_4$: 400.1049).

3,8-Dimethyl-3-(3-methyl-2-butenyl)bicyclo[3.3.0]octan-2-one (57) and 3,8-dimethyl-3-(3-methylbutyl)bicyclo[3.3.0]octan-2-one (58)

To a suspension of 16 g of Raney nickel (W-2) in 50 ml of benzene , was added a solution of 985 mg (2.463 mmol) of 56 in 60 ml of benzene. The reaction mixture after stirring at room temperature for 20 hr was filtered and the residue washed with ether. Concentration of the filtrate gave an oil which was chromatographed on silica gel using a solution of 30% benzene in n-pentane as eluent to give 56 mg (10%) of 58 : ir (film) 1730 cm^{-1} (ketone); nmr (CCl_4) τ 9.17 (s, 3 H, $-CH_3$), 9.08 (d, 6 H, J = 4 Hz, $(C\underline{H}_3)_2CH-$), 8.22 (d, 3 H, J = 6 Hz, $-CH_3$) and 7.49-7.16 (m, 1 H, $-\overset{|}{C}HCO-$); mass spectrum M^+ 222.1976 (Calcd. for $C_{15}H_{26}O$: 222.1984). Further elution with the same solvent afforded 230 mg (43%) of 57 : ir (film) 1730 cm^{-1} (ketone); nmr (CCl_4) τ 9.07 (s, 3 H, $-CH_3$), 8.93 (3 H, J = 6 Hz, $-CH_3$), 8.42, 8.29 (both s, 3 H each, $(CH_3)_2C=$) and 4.96 (t, 1 H, J = 7 Hz, =CH-); mass spectrum M^+ 220.1829 (Calcd. for $C_{15}H_{24}O$: 220.1827).

3,8-Dimethyl-3-(3-methyl-2-butenyl)bicyclo[3.3.0]octan-2-ols (59 and 59a)

At 0°C, lithium aluminum hydride (25 mg, 0.66 mmol) was slowly added to a stirred solution of 57 (132 mg, 0.6 mmol) in ether (20 ml). Stirring was continued under an atmosphere of nitrogen at room temperature overnight. After which time, water and saturated aqueous ammonium chloride (5 ml each) were added. The mixture was extracted with methylene chloride (4 X 25 ml). The extracts were washed with saturated sodium chloride solution , combined, and worked up in the usual manner. The residue was subjected

to silica gel column chromatography using a solution of 30% benzene in n-pentane as eluent to give 24 mg (18%) of 59a : ir (film) 3370 cm^{-1} (alcohol); nmr (CCl_4) τ 9.07 (s, 3 H, $-CH_3$), 9.06 (d, 3 H, J = 6 Hz, $-CH_3$), 8.42, 8.30 (both s, 3 H each, $(CH_3)_2C=$), 6.43 (d, 1 H, J = 6 Hz, $-\underline{C}HOH$), and 4.89 (t, 1 H, J = 7 Hz, =CH-); mass spectrum m/e (M - 17) 205.1957 (Calcd. for $C_{25}H_{25}$: 205.1957). Further elution with a solution of benzene - n-pentane (1:1) gave 101 mg (76%) of 59 : ir (film) 3360 cm^{-1} (alcohol); nmr (CCl_4) τ 9.09 (s, 3 H, $-CH_3$), 9.03 (d, 3 H, J = 6 Hz, $-CH_3$), 8.37, 8.28 (both s, 3 H each, $(CH_3)_2C=$), 6.77 (d, 1 H, J = 8 Hz, $-C\underline{H}OH$) and 4.84 (t, 1 H, J = 7 Hz, =CH-); mass spectrum m/e (M - 17) 205.1929 (Calcd. for $C_{15}H_{25}$: 205.1957).

3,8-Dimethyl-3-(3-methyl-2-butenyl)-2-tosylbicyclo[3.3.0]octane (60)

A solution of 59 (22 mg, 0.1 mmol) and p-toluenesulfonyl chloride (160 mg, 0.84 mmol) in pyridine (1 ml) was stirred at room temperature for 20 hr. Water (10 ml) was added and stirring was continued for 15 hr. The mixture was extracted with methylene chloride (3 X 15 ml) and the extracts were washed with saturated aqueous sodium bicarbonate, 2 N HCl and water (15 ml each). The organic solution was dried, filtered and concentrated to give an oil which was chromatographed on silica gel. Elution with a solution of 10% benzene in n-pentane gave rise to 17 mg (45%) of 60 : ir (film) 1600 and 1495 cm^{-1} (aromatic); nmr (CCl_4) τ 9.21 (d, 3 H, J = 6 Hz, CH_3-), 9.18 (s, 3 H, $-CH_3$), 8.42, 8.32 (both s, 3 H each, $(CH_3)_2C=$), 7.56 (s, 3 H, $C\underline{H}_3C_6H_4-$), 5.76 (d, 1 H, J = 8 Hz, -CHO-), 4.93 (t, 1 H, J = 7 Hz, =CH-) and 2.71, 2.24 (both d, 2 H each,

$J = 8$ Hz, aromatic hydrogens); mass spectrum m/e (M - 172) 204.1876 (Calcd. for $C_{15}H_{25}$: 204.1878).

2-Acetoxy-3,8-dimethyl-3-(3-methyl-2-butenyl)bicyclo[3.3.0]octane (61)

To a solution of 59 (22 mg, 0.1 mmol) in 0.5 ml of pyridine, was added 0.3 ml of acetic anhydride. The resulting solution, after standing in dark at room temperature for 19 hr, was concentrated. The residue was chromatographed on silica gel using a solution of 20% benzene in n-pentane as eluent giving 19 mg (72%) of 61 : ir (film) 1740 cm^{-1} (ester); nmr (CCl_4) τ 9.13 (s, 3 H, $-CH_3$), 9.12 (d, 3 H, $J = 6$ Hz, $-CH_3$), 8.3, 8.4 (both s, 3 H each, $(CH_3)_2C=$), 8.01 (s, 3 H, $-COCH_3$), 5.38 (d, 1 H, $J = 8$ Hz, $-\overset{|}{C}HO-$) and (t, 1 H, $J = 7$ Hz, $=CH-$).

2-Acetoxy-3,8-dimethyl-3-(3-formyl-2-butenyl)bicyclo[3.3.0]octane (62)

A solution of 61 (19 mg, 0.072 mmol) and selenium dioxide (32 mg, 0.29 mmol) in 3 ml of 95% ethanol was refluxed under an atmosphere of nitrogen for 15 hr. The reaction mixture was cooled to room temperature, filtered, diluted with water (15 ml) and extracted with ether (4 X 15 ml). The ether extracts were washed with saturated aqueous sodium bicarbonate and sodium chloride solution (15 ml each). Work-up of the organic solution in the usual manner gave an oily product which was chromatographed on silica gel. Elution with a solution of 30% benzene in n-pentane gave 5 mg (26%) of starting material 61. Further elution with benzene afforded 12 mg (81% based on the consumed material) of 62 : ir (film) 1740 (ester), 2820, 2720, 1690 (aldehyde) and 1645 cm^{-1} (double bond); nmr (CCl_4) τ

9.10 (d, 3 H, J = 6 Hz, $-CH_3$), 9.01 (s, 3 H, $-CH_3$), 8.24 (s, 3 H, $CH_3\overset{|}{C}=$), 8.0 (s, 3 H, $-COCH_3$), 7.62 (d, 2 H, J = 7 Hz, $=CHC\underline{H_2}-$), 5.31 (d, 1 H, J = 8 Hz, $-\overset{|}{C}HO-$), 3.56 (t, 1 H, J = 7 Hz, =CH-), and 0.65 (s, 1 H, -CHO); mass spectrum M^+ 278.1869 (Calcd. for $C_{17}H_{26}O_3$: 278.1882).

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